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I could not have completed this second edition without the support of my loving family: Audrey, Eric Jr., Sophie, and Isabelle.
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Preface

This book is designed to provide the readership with a single reference for the management of head and neck cancer and contemporary approaches to reconstruction of the surgical defect. While many texts address either ablative treatment or reconstruction, this work provides a single source for both disciplines. *Head and Neck Cancer: Management and Reconstruction* is a combination and thorough update of two prior texts, *Reconstruction of the Head and Neck: A Defect-Oriented Approach*, and *Head and Neck Cancer: An Evidence-Based Team Approach*. Written by internationally renowned experts, this book has been organized anatomically. Each chapter covers a broad range of head and neck sites including the oral cavity, pharynx, larynx, skin, and others. Each disease-based chapter is followed by a paired chapter on the reconstructive considerations. The chapters are organized by disease management concepts followed by a chapter the principles of reconstruction and functional rehabilitation. The illustrations and photos have been carefully chosen to depict concepts that are challenging to convey in the written text. They demonstrate surgical technique and the fine points associated with the complex anatomical characteristics of the head and neck. Each chapter reflects the authors’ personal experiences and approaches to treatment and reconstruction. The authors have been encouraged to explain their rationale for treatment approaches and reconstructive considerations. Many chapters conclude with case studies that highlight the important or controversial areas of management.

This book is designed as a thorough clinical review for the practicing surgeon, surgeon in training, and physician extenders who desire a single comprehensive resource. This is not an encyclopedic resource but one that is focused on the practical considerations for the management and reconstruction of patients with head and neck disease. As the editor and a contributor, I have established “editor’s notes” throughout each chapter highlighting important points and considerations. The tables and staging charts are formatted in way that is easy to understand and emphasizes only the most pertinent information. *Head and Neck Cancer: Management and Reconstruction* is a concise text that organizes a litany of information into a single manageable text.
Acknowledgments

The last four decades have given rise to enormous progress in the specialties of head and neck oncology and reconstruction. Without the accomplishments and instruction of the pioneers in the field, our patients would languish. This book acknowledges those pioneers and the young authors who have contributed to this work and represent the future of head and neck surgery. I would also like to acknowledge Thieme Publishers for their integrity and dedication to medical education.
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1 Carcinoma of the Oral Tongue and Floor of Mouth
Evan M. Graboyes and Brian Nussenbaum

1.1 Introduction
Treatment paradigms for oral tongue and floor of mouth (FOM) carcinoma remain primarily surgically based, with additional postoperative therapy directed by pathologic features. Despite the central role of the head and neck surgeon, optimal outcomes require a multidisciplinary team of otolaryngologists, radiation oncologists, medical oncologists, radiologists, pathologists, speech-language pathologists, maxillofacial prosthodontists, audiologists, and nutritionists. This chapter discusses the epidemiology of oral tongue and FOM carcinoma, relevant anatomy, etiologic factors, clinical presentation, diagnostic evaluation, treatment, oncologic outcomes, and prognosis. At its conclusion, two clinical cases are provided to help illustrate key points.

1.2 Epidemiology
1.2.1 Incidence
The oral tongue and FOM are the most commonly affected subsites of oral cavity squamous cell carcinoma (OCSCC), accounting for 37 to 53% and 17 to 25% of OCSCC, respectively.1,2,3 The incidence of oral tongue squamous cell carcinoma (SCC), and OCSCC overall, has been declining in the United States.4 The majority of patients are middle-aged or elderly, Caucasian, and male.2 A subset of patients with oral tongue SCC are Caucasian, female, under the age of 40, and without traditional risk factors.1 The incidence of oral tongue SCC in young Caucasian females has been steadily increasing, although the molecular basis or causal factor is not known.4

Note
The incidence of oral tongue SCC in young Caucasian females has been steadily increasing. The cause of the increase is unknown.

1.3 Anatomy of the Oral Tongue and Floor of Mouth
1.3.1 Neurovascular and Muscular Anatomy
Knowledge of the neurovascular and muscular anatomy of the oral tongue is critical for proper oncologic management. The tongue's major arterial supply is via the lingual artery. Originating from the external carotid artery as a separate branch or as a common lingual-facial trunk, it travels deep to the hypoglossus muscle and branches into the deep lingual, dorsal lingual, and sublingual arteries. The sublingual, deep lingual, and dorsal lingual veins drain the ventral, lateral, and dorsal aspects of the oral tongue into the internal jugular vein. The venae comitantes of the hypoglossal nerve (ranine veins) drain the tip of the oral tongue and travel along the lateral aspect of the hyoglossus muscle in close proximity to the hypoglossal nerve. All of the tongue muscles are innervated by the hypoglossal nerve except for the palatoglossus, which is supplied by the vagus nerve. The hypoglossal nerve travels lateral to the external carotid artery, then runs with its venae comitantes just superficial to the hypoglossus muscle and deep to the mylohyoid muscle to innervate the tongue muscles. The lingual nerve (cranial nerve [CN] V3) carries sensation from the oral tongue and taste fibers of the tongue. The extrinsic tongue muscles (genioglossus, hyoglossus, styloglossus, and palatoglossus) move the tongue in a rotational way to the tongue (Fig. 1.1). The oral tongue consists of four intrinsic and four extrinsic muscles. The intrinsic tongue muscles (superior longitudinal, inferior longitudinal, transverse, and vertical), which are not anchored to bone, change the tongue's shape. The extrinsic tongue muscles (genioglossus, hyoglossus, styloglossus, and palatoglossus) move the tongue in the oral cavity.

The FOM is a mucosal-lined space overlying the mylohyoid and hypoglossus muscles. The mylohyoid muscle is innervated by the nerve to the mylohyoid, a branch of the inferior alveolar nerve (CN V3). The lingual nerve provides general sensation from the region. The sublingual gland lies in the lateral FOM, and the papilla of the submandibular duct are located in the anteromedial FOM on either side of the lingual frenulum.

1.3.2 Lymphatic Drainage
The primary lymphatic drainage for the oral tongue and FOM is to the submental (level IA), perifacial (pre- and postvascular), subdigastric (or periglandular) (level IB), and jugulodigastric lymph nodes (level IIA). The anterior oral tongue preferentially drains to level IA, whereas the lateral tongue drains primarily to levels IB and IIA. There is controversy about the possibility of skip metastases from oral tongue tumors to the inferior jugular lymph nodes without proximal metastases. Byers et al suggested that 16% of patients with oral tongue SCC had metastases to level III or IV as the only manifestation of regional disease. Follow-up studies, however, suggested that level IV is not a primary nodal basin and that oral tongue SCC does not metastasize to level IV without more proximal metastasis. Oral tongue tumors, unlike base of tongue tumors, are low risk for draining to the contralateral neck unless the tumor approaches midline. The lymphatic supply from the FOM drains primarily to the submental and submandibular lymph nodes and there is a high propensity for bilateral drainage.

Note
The anterior oral tongue preferentially drains to lymph node level IA, whereas the lateral tongue drains primarily to levels IB and IIA.
1.4 Pathology

More than 90% of oral tongue and FOM malignancies are SCC or its variants (e.g., spindle cell, verrucous, basaloid, adenosquamous, etc.). Spindle cell carcinoma, when it occurs in the oral cavity, is most commonly located on the tongue and FOM. It has a significantly worse disease-specific survival (DSS) relative to conventional OCSCC. Although controversial, it is believed that these tumors are relatively radioresistant. Verrucous carcinoma (VC) is a low-grade SCC variant most commonly located in the oral cavity. It has a characteristic heaped up papillary appearance on physical examination and a low risk of regional metastases (Fig. 1.4). Historically, VC was considered resistant to radiation therapy (RT), although this remains a point of continued controversy. Other non-SCC malignant histology include minor salivary gland tumors (mucoepidermoid carcinoma, adenoid cystic carcinoma, etc.), lymphoma, sarcomas (leiomyosarcoma, rhabdomyosarcoma, etc.), and mucosal melanomas.

1.5 Risk Factors/Etiology

1.5.1 Tobacco and Alcohol

The majority of tumors of the oral tongue and FOM are related to alcohol and tobacco abuse. The risk is proportional to the quantity and duration of abuse for both, and there is a synergistic effect when used in combination. The FOM appears especially sensitive to tobacco and alcohol, possibly due to the sump effect of the pooling carcinogens in saliva. Despite the association between tobacco, alcohol, and oral tongue/FOM SCC, there has been a decrease in the rate and amount of tobacco and alcohol use in patients with OCSCC over time.

Note

The FOM appears especially sensitive to tobacco and alcohol, possibly due to the pooling carcinogens in saliva.

1.5.2 Chronic Dental Trauma

Chronic dental trauma from sharp teeth or rough edges has been linked to an increased risk of oral tongue cancer, especially lateral oral tongue (Fig. 1.5). An association between chronic denture rubbing and FOM SCC has also been described. The causal link between dental trauma and carcinogenesis is uncertain, but is hypothesized to occur through chronic inflammation.
While alcohol and tobacco are the most common causes of oral cancer, chronic dental trauma from sharp teeth or rough edges has also been linked to an increased risk of oral tongue cancer, especially lateral oral tongue cancer.

1.5.3 Oral Lichen Planus

Oral lichen planus (OLP) is a T-cell–mediated autoimmune disorder affecting the oral cavity mucosa that carries an increased risk of oral tongue and FOM SCC (Fig. 1.6). OLP is thought to have a 0.4 to 5% risk of malignant degeneration into OCSCC, although the precise risk remains controversial, as many OLP lesions are thought to be dysplastic lesions with a lichenoid appearance (oral lichenoid lesions) that are mistaken for OLP clinically and/or histologically. Subtypes of OLP include reticular (most common), erosive, atrophic, plaque, and bullous; the risk of malignant degeneration is thought to be highest in the erosive and atrophic forms. The classic findings on examination are lacy white lines (Wickham's striae). It is not uncommon for nonsmoking, nondrinking patients with multiply recurrent oral SCC to have OLP.

1.5.4 Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia (PVL) is a form of oral leukoplakia with a high risk of malignant degeneration (up to 64%). PVL is more common in females and nonsmokers, and lesions most frequently occur on the oral tongue, gingiva, and buccal mucosa. On examination, it is characterized by diffuse, verrucous white plaques that evolve into erythematous, exophytic lesions (Fig. 1.7). Treatment most commonly involves surgery and recurrence rates exceed 70%. 

Fig. 1.2 Lymphatic drainage of the floor of the mouth. Malignancy of the anterior floor of the mouth first drains into level IA. More advanced disease drains posterior along the floor of the mouth into the level IB lymph nodes. The posterior two-thirds of the floor of the mouth drains into the posterior system, which drains into level II lymph nodes.
Fig. 1.3 The primary drainage pattern of the lateral oral tongue. Lymphatic drainage is primarily into levels II and III.

Fig. 1.4 Verrucous carcinoma is a low-grade squamous cell carcinoma variant most commonly located in the oral cavity. It has a characteristic heaped-up papillary appearance on physical examination (arrow).

Fig. 1.5 Chronic dental trauma from sharp teeth or rough edges (black arrows) has been linked to an increased risk of oral tongue cancer, especially lateral oral tongue cancer (green arrow).
1.5.5 Fanconi’s Anemia

Fanconi’s anemia (FA) is an autosomal recessive disorder of DNA repair that, among other manifestations, carries a significantly increased risk of oral tongue and FOM SCC.18 These patients have an approximately 500-fold increased risk of head and neck cancer, with the oral tongue being the most common subsite.18 Patients with FA-related head and neck SCC present with a median age of 31 years and a 2:1 female predominance.18 In patients under the age of 40 without risk factors presenting with OCSCC, a cancer syndrome such as FA should be considered.18

1.6 Staging

Squamous cell carcinoma of the oral tongue and FOM is staged according to the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging classification for oral cavity.19 The seventh edition (2010) classifications are displayed in Table 1.1 and Table 1.2.19

The eighth edition, which was published in 2017 and took effect in 2018, is displayed in Table 1.3 and Table 1.4.20 Major changes for oral cavity cancer between the seventh and eighth editions of the AJCC staging manual include (1) use of depth of invasion (DOI) to determine T category, (2) removal of extrinsic tongue muscle invasion from the definition of T4a category, and (3) inclusion of extranodal extension (ENE) in the N category.20

1.7 Clinical Presentation

1.7.1 History

Patients with oral tongue and FOM SCC tend to present with early symptoms, and thus at an early T stage. Approximately 66 to 78% of patients with oral tongue SCC21,22 and 65 to 77% of patients with FOM SCC23,24 present with cT1–2 disease.
Carcinoma of the Oral Tongue and Floor of Mouth

Table 1.2 7th Ed (2010) American Joint Committee on Cancer (AJCC) tumor, node, metastasis staging classification for oral cavity cancer

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Tumor stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none &gt; 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>


Table 1.3 8th Ed (2017) American Joint Committee on Cancer (AJCC) tumor, node, metastasis staging classification for oral cavity carcinoma

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2 cm, ≤ 5 mm DOI</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor ≤ 2 cm, DOI &gt; 5 mm and ≤ 10 mm, or tumor &gt; 2 cm but ≤ 4 cm, and ≤ 10 mm DOI</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 4 cm or any tumor &gt; 10 mm DOI</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease*</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
</tbody>
</table>


Abbreviations: DOI, depth of invasion.

*Superficial erosion of bone/tooth socket (alone) by gingival primary is not sufficient to classify a tumor as T4.

1.7.2 Physical Examination

Goals of the physical examination include accurately staging the tumor and planning the extent of resection. Morphologically, SCC of the FOM and oral tongue tend to be necrotic ulcerative lesions, although they can have endophytic (Fig. 1.8) or exophytic patterns (Fig. 1.9). The most common location for oral tongue SCC is the posterolateral oral tongue, followed by the anterior and ventral tongue. Local spread for oral tongue SCC can occur medially across the central raphe to the contralateral side, posteriorly into the base of tongue, inferiorly into the suprahypoglossal muscles, or anteriorly or laterally into the FOM. For FOM tumors, local spread occurs into the adjacent mandible, posteriorly into the tongue, or deep through the FOM into the submandibular or sublingual spaces of the neck. Mobility of the tumor relative to adjacent structures is key to assess when planning the extent of resection. Examination of the tongue should include an assessment of mobility, as deviation can indicate involvement of the ipsilateral hypoglossal nerve, especially in the setting of tongue fasciculations and hemitongue atrophy. Tongue fixation can also occur in FOM SCC with extension into intrinsic tongue muscles. The relationship of the tumor to midline should be noted, as this will help determine the need for management of the contralateral neck.

A complete head and neck examination, including cranial nerves, and an evaluation of dentition are necessary in all patients with oral tongue or FOM SCC. Special attention to the hypoglossal nerve, mental nerve, and inferior alveolar nerve is necessary, and clinical concern for large nerve PNI should prompt magnetic resonance imaging (MRI) to assess for radiographic extent. Assessment of the patient’s dentition is important because chronic dental trauma may be the etiology of the malignancy in a nonsmoker. Evaluation of the dentition will allow for appropriate planning in the operating room if dental extractions are required for oncologic reasons. Furthermore, patients with locoregionally advanced tumors for whom adjuvant radiation is expected.

Note
NCCN guidelines suggest considering placing a prophylactic feeding tube in patients with severe weight loss: 5% in the prior month or 10% in the prior 6 months.

evaluation. Comorbid conditions can impact the timing of diagnosis, selection of treatment, and prognosis. Medical conditions or medications causing immunosuppression are important to note as these patients have a worse prognosis.
can have dental extractions planned to prevent untimely delay in the initiation of postoperative therapy. The neck should be palpated for evidence of regional metastases and the size, location, and mobility of lymph nodes noted for accurate clinical regional staging.

**Note**

Patients who present with motor or sensory deficits should undergo an MRI to determine the extent of perineural disease. MRI may demonstrate nerve enhancement when extensive PNI is present.

Inspection of other head and neck mucosal sites for synchronous second primary tumors, either in the oral cavity or elsewhere in the upper aerodigestive tract, is recommended. Synchronous second primary tumors occur in 2 to 3% of patients with oral tongue and FOM SCC. For oral tongue and FOM SCC, the risk of a synchronous second primary tumor is higher in patients with a history of tobacco use relative to those who never used tobacco.

### 1.8 Diagnostic Evaluation

#### 1.8.1 Biopsy

If not previously obtained, an incisional biopsy can be performed to get tissue for histopathologic diagnosis in clinic under local anesthesia or in the operating room. If the biopsy has already been performed at an outside institution, the slides should be reviewed at the treating hospital. If a biopsy of the primary is challenging in clinic and the patient has evidence of regional metastasis, an ultrasound (US)-guided fine-needle aspiration (FNA) of the neck mass can be performed.

#### 1.8.2 Imaging

Ultrasound, CT, MRI, and PET-CT play complementary roles in the diagnostic evaluation of FOM and oral tongue SCC, and none, some, or all of these imaging modalities may be employed in the preoperative evaluation based in part on tumor characteristics and in part on institutional preference. NCCN guidelines for OCSCC recommend a CT with contrast and/or MRI with contrast of the primary and neck as indicated, and consideration of a PET/CT for patients with stage III–IV disease. Cross-sectional imaging can help clinically stage the tumor, assess extent and invasion into adjacent structures, establish proximity to the midline, and identify perineural spread. For locally advanced oral tongue and FOM SCC, imaging can demonstrate invasion of the mandible, which would upstage the patients to cT4a. Cross-sectional imaging can also determine the presence, location, size, and number of suspicious lymph nodes for accurate regional staging. Approximately 40% of patients with oral tongue SCC and 50% of FOM SCC present with clinical-radiologic evidence of regional metastases.

#### 1.8.3 Ultrasound

Ultrasound can be used to assess tumor thickness and the presence of regional metastases. Tumor thickness is measured from the tumor’s surface to the deepest portion of the hypoechogenic acoustic shadow. Ultrasonographic tumor thickness correlates with pathologic tumor thickness in 96 to 98% of patients with tumors 3- to 5-mm thick and may be more accurate than MRI.

**Note**

Tumor thickness by ultrasound correlates with pathologic tumor thickness in 96 to 98% of patients with tumors 3- to 5-mm thick and may be more accurate than MRI.
1.8.4 Computed Tomography

Contrast-enhanced CT is often employed in the evaluation of SCC of the oral tongue and FOM. Key findings of mandible invasion on CT scan include cortical erosion or mandible destruction. CT has a higher specificity and positive predictive value (PPV) than MRI for detecting mandibular invasion, and in some studies the PPV of CT approaches 100%. Its sensitivity and negative predictive value (NPV) are, however, lower than MRI. CT can also be used for virtual surgical planning and fabrication of patient-specific prebent reconstruction plates for patients undergoing segmental mandibulectomy. CT can be limited by dental amalgam and subsequent streak artifact. One solution to this problem is to reorient the gantry to acquire images parallel to the plane containing the metal.

1.8.5 Magnetic Resonance Imaging

MRI with gadolinium provides complementary information to CT. Some prefer MRI for oral tongue SCC because it allows a better assessment of the infiltration between muscle fibers of the tongue than CT. With regard to detection of mandible invasion, MRI has superior sensitivity but decreased specificity and PPV relative to CT. A negative MRI can therefore reliably exclude mandibular invasion, but use of MRI alone will result in a high rate of false positives in which mandibles without pathologic tumor invasion are interpreted as having invasion on MRI. The high rate of false-positive MRI scans for identifying mandibular invasion is attributed to chemical shift artifact from bone marrow fat. Another potential benefit of MRI in evaluating patients with oral tongue or FOM SCC is superior detection of perineural spread along the inferior alveolar, lingual, or hypoglossal nerves. Fat-suppressed, T1, postcontrast imaging can demonstrate nerve enhancement of the affected nerve. Chronic denervation atrophy of the affected muscle can manifest as a hyperintense signal on T1 and T2 sequences due to fatty replacement. It is critical to detect perineural spread along large nerves preoperatively in order to determine whether there is intracranial extent (usually along CN V3 through foramen ovale), thus making the disease locally unresectable.

1.8.6 Positron Emission Tomography/Computed Tomography

For patients with oral tongue and FOM SCC, PET/CT can be utilized in the pretreatment evaluation for assessment of regional metastases, distant metastases, and synchronous second primary tumors. Current NCCN guidelines suggest that it be considered for patients with stage III–IV disease. Detection of metastatic disease by PET/CT requires a metastasis that is at least 5 x 5 x 5 mm in size. Its marginal benefit in staging regional disease for patients with oral cavity SCC that are clinically-radiographically N0 by CT or MR is limited, with a sensitivity of 67% and a specificity of 85% relative to final pathology in elective neck dissection (END). Most authors agree that it is not accurate enough to guide therapeutic decision making in the cN0 neck. PET/CT is highly sensitive in the detection of distant metastasis (DM) or synchronous primary malignancies, most commonly in other subsites of the head and neck, lung, or esophagus. PET/CT has been assessed as a way of determining mandibular invasion and does not appear to have a significant benefit relative to CT.

1.8.7 Pathology

Pathologic information from the biopsy or the definitive surgical resection is critically important to determine proper adjuvant therapy and prognosis. Crucial pieces of information from the primary specimen include margin status, depth of invasion, grade, PNI, lymphovascular space invasion (LVSI), and histologic subtype. Depth of invasion and tumor thickness are technically not synonymous, although the terms are often used interchangeably. Depth of invasion is defined as the extent of cancer growth into a tissue beneath an epithelial surface. It is measured by drawing a horizontal line at the level of the basement membrane of the closest adjacent normal mucosa and dropping a vertical line from the horizon line to the deepest aspect of the tumor. Tumor thickness, on the other hand, refers to the thickness of the entire tumor mass as measured.
from the most superficial aspect of the tumor to the depth of the tumor. When a tumor is ulcerative with no overlying epithelium, depth of invasion will be greater than tumor thickness. When a tumor is exophytic due to hyperkeratosis, depth of invasion will be less than tumor thickness (> Fig. 1.11). Despite the confusion regarding practicalities of measurement, both tumor thickness and depth of invasion are important to know because they affect the risk of regional metastases, locoregional recurrence, and survival. Depth of invasion is now incorporated into the T category in the eighth edition of the AJCC staging for oral cavity cancer.

**Note**

Depth of invasion is one of the most important prognosticators because it impacts the risk of regional metastases, locoregional recurrence, and survival. Depth of invasion is now incorporated into the T category for staging oral cavity cancer.

A histologic risk assessment model described by Brandwein-Gensler et al for OSCC incorporates information about PNI, worst pattern of invasion (WPOI), and lymphocyte host response (LHR). WPOI describes the manner in which the cancer infiltrates tissue at the tumor/host interface and ranges from a broad pushing front of tumor (good prognosis) (> Fig. 1.12a) to infiltrative satellite islands of tumor (worse prognosis) (> Fig. 1.12b). The model has independent prognostic significance (> Fig. 1.12c).

### 1.8.8 Genetic Testing

Genetic testing is not routinely indicated for patients with oral tongue or FOM SCC, but patients less than 40 years of age without risk factors could consider genetic testing for FA. FA is diagnosed by demonstrating chromosomal fragility by culturing patient’s cells with mitomycin C or diepoxybutane. Knowledge of FA status is important because, in addition to the obvious effect on family planning, it informs decisions about
adjuvant therapy, as FA patients have a high rate of morbidity and mortality with radiation or chemotherapy.18

1.9 Treatment

Treatment of oral tongue and FOM SCC is a primary surgery-based paradigm with pathology-directed adjuvant therapy.25 In general, stage I–II tumors can be treated with single modality (surgical) therapy, whereas stage III–IV tumors require multimodality therapy, usually with surgery followed by postoperative radiation or chemoradiation (CRT).

1.9.1 Surgery

Primary Tumor

For the primary tumor, treatment planning requires determination of an approach, extent of resection, and reconstruction. Commonly employed approaches for oral tongue and FOM SCC include the transoral approach, visor, lip split/mandibulotomy (Fig. 1.13a–c), and lingual release and transcervical pull-through (Fig. 1.14). A transcervical approach with lingual release and pull-through may facilitate access to the posterior oral tongue while obviating a mandibulotomy. The approach to the primary is dictated by tumor factors (e.g., tumor size and location), patient factors (e.g., trismus, dentition, neck morphology, etc.), and possibly reconstructive requirements (e.g., free flap inset). In general, early T stage can be managed transorally, whereas locally advanced (T3–4) tumors may require a more extended approach.

Locally advanced FOM or oral tongue SCC may require either a marginal or segmental mandibulectomy when the tumor is adherent to or invading the mandible. The extent of the mandible resection is determined by physical examination, radiologic evaluation, and intraoperative findings.48 A general rule of thumb in dentulous patients who have not had prior RT is to resect one layer deeper than the tumor is invading. In a dentulous patient without prior RT in whom the tumor is adherent to the lingual aspect of the mandibular periosteum but without gross mandible invasion, marginal mandibulectomy with examination of the underlying lingual cortex of the mandible...
can be performed. If the lingual cortex is grossly normal, a rim mandibulectomy is an oncologically sound operation ([Fig. 1.15]). When frank invasion of the mandible is apparent from preoperative examination, imaging, or intraoperative findings, a segmental mandibulectomy is recommended. NCCN guidelines recommend a segmental mandibulectomy if there is medullary space invasion. Most agree that segmental mandibulectomy should be strongly considered when the tumor abuts the mandible in previously irradiated patients ([Fig. 1.16]). Finally, marginal mandibulectomy requires preservation of at least 10 mm of mandible height to prevent pathologic fractures. In patients for whom marginal mandibulectomy would leave the patient with less than 10 mm of mandible height, segmental mandibulectomy is recommended.

**Note**

A segmental mandibulectomy should be strongly considered when the tumor abuts the mandible in previously irradiated patient and in patients for whom marginal mandibulectomy would leave the patient with less than 10 mm of mandible height.

The importance of negative margins for oral tongue and FOM SCC is recognized by most as having prognostic significance. The practicalities of margin analysis, specifically whether to take the margin from the tumor specimen or the surgical defect, remain controversial. A prospective, randomized trial of 71 patients with OCSCC (36% oral tongue or FOM) comparing specimen- and patient-driven margins found that specimen-driven margins resulted in a higher rate of intraoperative re-resection for close or positive margins, a higher rate of wide margins on final pathologic analysis, and a decreased rate of postoperative adjuvant therapy escalation because of margin status. There is retrospective, nonrandomized evidence that in early-stage oral tongue SCC, sampling margins from the tumor bed instead of the glossectomy specimen is associated with worse local control.

A separate issue regarding margin analysis for oral tongue and FOM SCC is the prognostic significance and management implications of microscopic tumor cut-through (i.e., an initial positive margin on intraoperative frozen section that is subsequently revised by re-resection to a negative-margin resection on final pathologic analysis). Head and neck surgeons remain divided as to whether this situation truly represents a negative margin. Some initial small studies suggested that for patients with OCSCC microscopic tumor cut-through was independently associated with worse local control and DSS. In a recent larger study of 547 patients with OCSCC (75% oral tongue or FOM), microscopic tumor cut-through was associated with worse local control and DSS on univariate analysis; however, this effect disappeared if patients were pathologically node positive. Because microscopic tumor cut-through was not associated with worse outcomes in node-negative patients, it is not viewed as an indication, unto itself, for adjuvant RT or escalation of therapy.

**Regional Metastasis**

Management of the neck for cN0 patients remains controversial. Patients who are cN0 can be managed with observation, END, sentinel lymph node biopsy (SLNB), or elective neck irradiation. Overall, early-stage oral tongue and FOM SCC have a high rate of occult regional micrometastatic disease, with studies reporting between 20 and 50%.
Some advocate for treatment of the neck for cT1–2N0 oral tongue and FOM SCC based on depth of invasion. Proponents of this approach recommend END for patients with cT1–2N0 oral tongue and FOM SCC with depth of invasion greater than or equal to 4 mm. When pathologic depth of invasion is 4 to 9 mm, the risk of occult micrometastatic disease is 17 to 44%. In one prospective randomized trial of 67 patients with cT1–2N0 oral tongue or FOM SCC randomized to END or observation, disease-free survival (DFS) was increased in the group with tumors greater than or equal to 4-mm deep. Patients with a tumor depth less than 2 mm do not require elective treatment of the neck as the risk of occult regional metastatic disease is less than 5%. For tumors that are 2–to 4-mm deep, NCCN guidelines recommend that the decision be tailored according to clinical judgment (related to reliability of follow-up, clinical suspicion, or other factors). The risk of occult metastatic regional disease in tumors with less than or equal to 3 mm pathologic depth is 6 to 8%. For patients who do undergo END for management of the cN0 neck for oral tongue and FOM SCC is SLNB. In a prospective, multi-institutional trial, 140 patients with cT1–2N0 OCSCC (85% oral tongue, 1% FOM) were randomized to END or observation with therapeutic neck dissection for nodal relapse. Patients in the END group had increased rates of 3-year overall survival (OS) (80 vs. 68%) and DFS (70 vs. 46%) relative to those receiving initial nodal observation. A post-hoc analysis did not show a survival benefit to END for patients with tumor depth of invasion less than or equal to 3 mm. An older prospective randomized controlled trial of patients with cT1–2N0 oral tongue SCC showed a benefit to END compared to observation, but only for patients with tumor depth greater than 4 mm. A third option for management of cN0 neck for oral tongue and FOM SCC is SLNB. In a prospective, multi-institutional trial, 140 patients with cT1–2N0 OCSCC (68% oral tongue, 1% FOM) underwent SLNB followed by immediate selective neck dissection (SND). For the patients who were pN0 by simultaneous neck dissection (ND), SLNB had an NPV of 96%. For patients who were pathologically node positive by simultaneous ND, SLNB had a true positive rate of 90%. SLNB is less accurate for FOM than oral tongue tumors. Proponents of SLNB argue that it is a better oncologic option than observation and has less morbidity than performing END on all patients. For patients who do undergo END for management of the cN0 neck, disagreement exists about the nodal levels at risk for occult metastases, especially for oral tongue. Most agree that level IIb is at a very low risk of occult metastatic disease in the cN0 patient and thus omission of this level is oncologically sound. Some advocate for removing levels I to IV based on a concern for skip metastases to level IV. Others, however, have shown that the risk of metastases to level IV is low in cN0 oral tongue SCC and that omitting level IV does not increase the risk of regional recurrence. These authors thus recommend removing levels I to III for cN0 SCC of the oral tongue and FOM. When SND I to III is performed for oral tongue or FOM SCC, inclusion of the jugulo-omohyoid nodes is imperative. The current NCCN recommendations for patients who are clinically node negative undergoing END in oral tongue or FOM SCC is to perform an SND of at least levels I to III. Management of the contralateral neck is based on the location of the primary and is recommended for tumors that approach within 1 cm of the midline.

Note

Patients who are clinically N0 can be managed with observation, elective neck dissection, sentinel lymph node biopsy, or elective neck irradiation. However, several factors should be considered including depth of invasion.

Preservation of the submandibular gland (SMG) during ND remains controversial. Proponents of SMG preservation point out that it does not contain lymph nodes, preservation of nonlymphatic structures was the basis of moving from radical to modified radical NDs, and that invasion of the SMG directly from OCSCC is rare. Advocates of SMG excision argue that complete removal of the pre- and postfacial lymph nodes with gland preservation is technically challenging and that SMG preservation for FOM or oral tongue SCC may increase the risk of regional recurrence.

For patients with clinical evidence of neck disease, the neck is generally managed with a therapeutic ND. The levels dissected and removal of nonlymphatic structures is based on disease extent. NCCN guidelines recommend selective or comprehensive ND for cN1–N2 disease and comprehensive ND for cN3 disease. For patients with clinical evidence of neck disease, especially when level Iia is involved, inclusion of Iib is merited.
1.9.2 Primary Nonsurgical Management

Primarily nonsurgical paradigms exist for patients with oral tongue or FOM SCC. Proponents advocate for nonsurgical alternatives for patients with T4a disease to avoid a large resection and reconstruction, unrecteable disease, poor operative candidates, or patient preference.79,80,81 Nonsurgical paradigms are generally associated with inferior oncologic outcomes.82,83 A study of patients with stage III/IV OCSCC comparing induction chemotherapy (IC) followed by chemoradiation for responders to primary surgery-based therapy showed decreased OS, DSS, and locoregional control with IC relative to upfront surgery.83 Primary nonsurgical management is associated with a high rate of late morbidity, specifically osteoradionecrosis (ORN) of the mandible, soft tissue fibrosis, dysphagia, and xerostomia.82 Definitive RT doses to the oral cavity have an 18% risk of developing clinically significant ORN of the mandible.79,80

Note
Surgery is recommended for oral cavity carcinoma because primary nonsurgical management is associated with a high rate of late morbidity.

1.10 Oncologic Outcomes

1.10.1 Patterns of Failure

For oral tongue and FOM SCC, local and regional failures occur with similar frequency and range from 14 to 31% for rates of local failure and 15 to 34% for regional failure.20,22,84,85,86 Most failures occur within the first 2 years.20,22,86 For FOM SCC, some authors report local failure as being twice as common as regional failures (41 vs. 19%).23 although others report local and regional recurrence rates that are more similar (20 vs. 26%).24 The 5-year rate of distant metastasis for OCSCC is approximately 10% and most commonly occurs to lung, bone, skin, and liver.95,86 The rate of DM is higher in patients with locoregional recurrence (21%) relative to those without locoregional failure (7%).85

1.10.2 Survival

Estimates of survival for various retrospective cohort series are displayed in ▶ Table 1.5. Five-year estimates of OS for oral tongue SCC range from 42 to 73% and 5-year estimates of DSS range from 57 to 71%.20,21,22,86,87,88,89 Outcomes for patients with early-stage (T1–2N0) oral tongue SCC are slightly better, with estimates of 5-year survival of 79% for OS, 86% for DSS, and 70% for DFS.66 Survival estimates for FOM SCC are similar to those of oral tongue, ranging from 46 to 65% for OS and 56 to 76% for DSS.23,24,30

1.11 Prognostic Factors

1.11.1 American Joint Committee on Cancer Tumor, Node, Metastasis Stage

American Joint Committee on Cancer TNM stage, especially the N stage, is independently prognostic across a variety of survival metrics for patients with oral tongue and FOM SCC.20,22,23,86,89,90,91 For patients with clinically early-stage (cT1–2N0) SCC of the oral tongue, the presence of occult metastasis has been identified as the strongest predictor of OS, DSS, and recurrence-free survival (RFS), decreasing the 5-year DSS from 85% for pN0 patients to 49% for patients with pathologic evidence of neck metastases.66

<table>
<thead>
<tr>
<th>Author</th>
<th>Study years</th>
<th>#</th>
<th>TNM stage distribution</th>
<th>5-y OS</th>
<th>5-y DSS</th>
<th>5-y DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aksu27</td>
<td>1987–2000</td>
<td>80</td>
<td>5 pT1, 35 pT2, 17 pT3, 4 pT4</td>
<td>42%</td>
<td>45%</td>
<td>-</td>
</tr>
<tr>
<td>Kokemueller22</td>
<td>1980–2009</td>
<td>341</td>
<td>150 pT1, 108 pT2, 31 pT3, 17 pT4</td>
<td>51%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kurokawa88</td>
<td>1985–1999</td>
<td>124</td>
<td>Not reported</td>
<td>-</td>
<td>-</td>
<td>67%</td>
</tr>
<tr>
<td>Mosleh-Shirazi89</td>
<td>1982–2007</td>
<td>102</td>
<td>14 pT1, 52 pT2, 29 pT3, 7 pT4</td>
<td>73%</td>
<td>-</td>
<td>66%</td>
</tr>
<tr>
<td>Okuyemi21</td>
<td>1995–2005</td>
<td>166</td>
<td>62 pT1, 57 pT2, 22 pT3, 20 pT4</td>
<td>58%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sessions86</td>
<td>1957–1996</td>
<td>332</td>
<td>116 cT1, 128 cT2, 71 cT3, 17 cT4</td>
<td>48%</td>
<td>57%</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival; TNM, tumor, node, metastasis.
1.11.2 Clinicopathologic Models
A number of authors have recognized the shortcomings of AJCC TNM staging for prognosis in oral tongue and FOM SCC. As a result, they have devised prognostic models that incorporate other clinical data in an attempt to improve survival prognostication in oral tongue and FOM SCC. One retrospective review of 166 patients with oral tongue SCC compared a clinicopathologic model composed of comorbidity (as measured by the Adult Comorbidity Evaluation-27 [ACE-27]), and determined that tumor dimension, ECS, and LVI were better at predicting survival than pathologic TNM staging.

Note
In patients with early-stage carcinoma of the oral tongue, the presence of occult metastasis is associated with a significant decrease in overall and disease-free survival.

1.11.3 Histologic Risk Assessment
The histologic risk assessment proposed by Brandwein–Gensler et al is composed of three variables: WPOI, PNI, and LHR. It is prognostic for local control and OS for patients with OCSCC across a variety of T stages and margin statuses, predictive of OS in patients with a variety of T stages with margin-negative resections, and associated with locoregional control and DSS for early stage OCSCC. The histologic risk assessment is strongly predictive of local disease-free and overall survival.

1.11.4 Margin Status
Positive margins have been associated with decreased measures of survival in a variety of studies of oral tongue SCC and FOM SCC. On the other hand, a positive margin was not associated with higher locoregional failure or worse OS for patients with OCSCC when factors such as the Brandwein–Gensler histologic risk assessment are considered.

1.11.5 Tumor Thickness and Depth of Invasion
Pathologic tumor thickness and depth of invasion are correlated with the risk of occult regional metastases in early T stage oral tongue and FOM SCC as well as locoregional recurrence and survival.

1.11.6 Perineural Invasion
Perineural invasion has been reported by some as having independent prognostic significance for OCSCC and oral tongue SCC in its relationship to regional metastases, recurrence, and survival.

1.11.7 Immunosuppression
For patients with OCSCC, immune compromise is an independent negative prognosticator for local control, OS, and DSS.

1.12 Conclusion
In summary, accurate clinical examination and diagnostic evaluation is key to successful management of patients with oral tongue and FOM SCC. Treatment of oral tongue and FOM SCC remains primarily surgical, with additional therapy directed by pathologic features. Management of the neck in the cN0 setting remains an area of controversy, but is often dictated by tumor thickness. Patients with pT1–2N0 SCC of the oral tongue and FOM have excellent oncologic outcomes and can be managed with single modality therapy whereas patients with locoregionally advanced disease require multimodality therapy.

1.13 Clinical Cases
1.13.1 Case 1: cT1N0 Squamous Cell Carcinoma of the Right Lateral Oral Tongue
Presentation
A 66-year-old woman with no tobacco history and a past medical history of oral leukoplakia was referred for evaluation of a new painful lesion on the oral tongue. She had been treated for thrush without any benefit. Prior to the referral, she underwent a biopsy of the lesion that revealed SCC, present at the margins. On examination, there was a 2 × 2 cm area of leukoplakia on the right lateral oral tongue but no palpable lymphadenopathy.

Diagnosis and Workup
A neck CT was performed that revealed a soft tissue defect from the prior biopsy and no evidence of regional disease. A PET/CT revealed a fluoro-2-deoxy-D-glucose (FDG)–avid lesion in the right lateral tongue and some mild FDG uptake in a level II lymph node.
lymph node that lacked an underlying anatomical correlate. Her tumor was staged as a cT1N0 SCC of the right oral tongue.

**Options for Treatment**

The options for treatment of her cT1N0 SCC of the right lateral oral tongue included a primary surgical approach with pathology-directed adjuvant therapy or primary radiation. Surgery at the primary site would consist of a partial glossectomy and reconstruction via healing by secondary intention, primary closure, acellular dermal graft, or split-thickness skin graft. For management of her neck, options included observation, END based on depth of invasion, END regardless of depth of invasion, or SLNB. The addition of adjuvant RT or CRT would be based on adverse histologic findings on final pathology. A nonsurgical option of radiation to the tongue and neck was discussed with the patient, as well as its expected oncologic results and morbidity.

**Treatment of the Primary Tumor and Neck**

Her outside hospital pathology slides were internally reviewed to confirm the diagnosis and her case was presented at the multidisciplinary head and neck tumor board conference. The recommended therapy was a primary surgical approach with pathology-directed adjuvant therapy. Her surgery consisted of a partial glossectomy via a transoral approach, primary closure and deferred management of the neck until final pathologic depth of invasion was established. Her final pathology returned with negative margins, a 2-mm depth of invasion, and no other adverse pathologic features. The tumor board discussed an ipsilateral neck dissection and nodal as options for management. Given the less than 10% risk of occult micrometastatic disease, the decision was made to proceed with nodal observation. No adverse features were noted at the primary site to indicate a need for adjuvant radiation.

1.13.2 Case 2: T4aN2c SCC of the Floor of Mouth

**Presentation**

A 72-year-old woman with a 50 pack-year history of tobacco use, diabetes, and stroke on aspirin and clopidogrel was referred to the multidisciplinary head and neck cancer clinic for evaluation of a painful sore in her floor of mouth. She noted it originally while placing her dentures and she can no longer wear the dentures because of the pain. Prior to the referral, she underwent a biopsy of the lesion that revealed SCC. On examination, there was an exophytic mass arising from the left anterior FOM extending onto the mandibular alveolus but not the ventral tongue. The patient was edentulous of her mandibular teeth but had a few remaining maxillary teeth. She had palpable lymphadenopathy in level Ib bilaterally.

**Diagnosis and Workup**

A neck CT was performed that revealed her FOM mass with associated bony destruction of the mandible (▶ Fig. 1.18) as well as pathologic appearing lymph nodes in level Ib bilaterally. Her PET/CT showed the FDG-avid FOM mass as well as enlarged FDG-avid submandibular lymph nodes bilaterally. There was no evidence of synchronous primary tumors or distant metastasis.

**Options for Treatment**

The options for treatment of her cT4aN2c SCC of the left FOM included a primary surgical approach with adjuvant radiation of chemoradiation based on final pathologic features or a primary nonsurgical approach of chemoradiation. Because of the cortical erosion of the mandible on her CT scan and her edentulous mandible, a segmental mandibulectomy would be required if she was treated surgically. An apron approach would provide the best access at the least morbidity for her composite resection with segmental mandibulectomy.

Regarding her regional metastases, it was felt that neck dissections of levels I to III bilaterally would be appropriate, with level IV included if more suspicious lymph nodes were found in level III intraoperatively. Her surgical option would thus consist of a composite resection with segmental mandibulectomy, bilateral neck dissections, tracheotomy, and osteocutaneous free flap reconstruction of her anterior segmental mandibulectomy defect. The patient was not felt to be a good candidate for nonsurgical therapy given her age, performance status, and bone invasion.

**Treatment of the Primary Tumor and Neck**

Her outside hospital pathology slides were internally reviewed to confirm the diagnosis and her case was presented at the multidisciplinary head and neck tumor board conference. The recommended therapy was a primary surgical approach with adjuvant RT or CRT based on final pathology. Her surgery consisted of an apron approach to composite oral cavity resection and left segmental mandibulectomy from left posterior body to right parasympysis, bilateral SND 1 to 3, tracheotomy, and left osteocutaneous scapula free flap. Final pathology returned with no PNI or LVSI, high-grade dysplasia at a medial soft tissue margin, and two metastatic lymph nodes without ECS. Her case was...
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Fig. 1.18 Axial CT scan image showing erosion of the mandible by the floor of mouth squamous cell carcinoma.

rediscussed in multidisciplinary tumor conference and it was recommended that she receive 66 Gy of adjuvant RT to the primary and both necks.

References

Carcinoma of the Oral Tongue and Floor of Mouth

2 Reconstruction of the Oral Tongue and Floor of Mouth

Rodrigo Bayon and Nitin A. Pagedar

2.1 Introduction

Despite its simple appearance, the tongue’s complex structure underscores its pivotal role in both speech and swallowing. Through a series of coordinated muscle movements, it is able to take on an array of shapes that allow for proper articulation. It is also critical for propulsion and delivery of a food bolus to the oropharynx to initiate swallowing. Its special sensory fibers convey taste, which allows us to derive pleasure from what we eat and also protects us from hazardous ingestion. The impact that loss of part of the tongue or all of the tongue can have on patients cannot be stressed enough. Consequently, a variety of techniques for reconstruction of the tongue have developed over many decades to attempt to recapitulate the form and function of the oral tongue.

Early attempts at reconstruction focused simply on closure of the oral cavity defect. This often resulted in suturing of the remnant tongue mucosa to surrounding tissues. When possible, skin grafts were used, however, the contracture that occurred would cause tethering of the tongue to the floor of mouth. As can be imagined, both of these options had a significant impact on the patient’s ability to speak and taking an oral diet. The 1960s–1980s brought about a new era in oral cavity reconstruction with the identification and use of multiple regional pedicled flaps. The introduction of free tissue transfer techniques and the refinement of their application to oral cavity reconstruction brought about further improvements in outcomes.

2.2 Relevant Anatomy

The tongue can be divided into two distinct subsites: the oral tongue and tongue base (which is discussed in Chapter 13). The anatomical boundary separating these two subsites is the sulcus terminalis, a V-shaped line that runs posterior to the circumvallate papillae and includes the foramen cecum. The tongue is lined by a stratified squamous epithelium studded with special sensory organs that contribute to taste and sensation. This mucosa is thickest on the dorsum and becomes thin and pliable as it transitions onto the floor of the mouth. The mucosal lining includes reflections onto the pharyngeal wall known as the glossoepithelial folds and a midline frenulum. Adjacent to this midline frenulum are the paired Wharton ducts that drain saliva from the submandibular and sublingual glands.

Underneath this lining is a complex of intrinsic and extrinsic tongue muscles. The intrinsic muscles are within the body of the tongue and include the superior and inferior longitudinal, transverse, and vertical muscles. These muscles allow for the multitude of shapes the tongue can take on to allow for articulation. The extrinsic tongue muscles arise outside of the body of the tongue and include the hyoglossus, genioglossus, styloglossus, and palatoglossus. These extrinsic muscles assist with elevation, depression, and protrusion of the tongue. All tongue muscles receive innervation from the hypoglossal nerve except palatoglossus, which is innervated by the vagus nerve. General sensation is provided by the lingual nerve, and special sensory (taste) innervation is derived from the chorda tympani nerve which merges with the lingual nerve in the infratemporal fossa. The tongue has a very robust blood supply derived primarily from the lingual arteries.

The floor of mouth is critical to normal function of the oral tongue. It is the mobile thin mucosal surface between the ventral tongue and the mandibular gingiva. The oral tongue, in the absence of intact floor of mouth, remains limited in its mobility. The mucosa of the floor of mouth overlies the sublingual glands and the Wharton ducts. The lingual nerve lies in a submucosal position at the lateral floor of mouth.

2.3 Evaluation of the Oral Tongue Defect

The plan for reconstruction follows from the surgeon’s assessment of the anatomy of the oncologic defect. A fairly small number of critical factors provides the constraints of the reconstructive problem. The size of the defect is the most obvious consideration; the surface area is a relevant concern, but the volume is even more important to understand. Involvement of the extrinsic muscles of the tongue, identified clinically or radiographically, correlates with a larger three-dimensional defect even without any change in the anticipated mucosal resection, while also removing functionally important soft tissue. Given the need to manage the cervical lymph nodes, extension of tumor into the extrinsic muscles, floor of mouth, sublingual gland, or mylohyoid may predict communication of the glossectomy defect with the submandibular triangle of the neck. In general, smaller resections leave more residual functional tongue, and reconstruction should aim at maximizing the function of the residual native tongue; moving toward total glossectomy, with progressively less functional muscle remaining, the surgeon should focus more on adding stable bulk to optimize the potential for swallowing function. Involvement of mandibular bone brings with it a variety of other considerations that are discussed in Chapter 10.

Note

Small defects of the oral tongue preserve residual functional tongue. Reconstruction should aim at maximizing the function of the residual native tongue as this will preserve movement, sensation, and function.

2.4 Reconstructive Goals and Assessment of Outcomes

Goals of reconstruction must inherently depend on the extent of the defect that is expected. Classification systems have been developed to describe, communicate, and compare defects and
Reconstruction of the Oral Tongue and Floor of Mouth

Table 2.1 The goals for reconstruction of a hemiglossectomy defect

<table>
<thead>
<tr>
<th>Goal</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>The tongue fills the volume between the gums, teeth, floor of mouth, and palate with the mouth closed.</td>
<td></td>
</tr>
<tr>
<td>The reconstructed tongue can protrude to contact the premaxilla.</td>
<td></td>
</tr>
<tr>
<td>The tongue is able to sweep the oral vestibule and protrude past the incisors.</td>
<td></td>
</tr>
<tr>
<td>Maximal sensation is preserved in both the native and reconstructed surfaces of the tongue.</td>
<td></td>
</tr>
</tbody>
</table>

reconstructive results. The simplest schema involves division of the tongue parasagittally into quarters, with additional considerations deriving from concurrent resection of mandible or tongue base.

The classification system of oncologic defects of the oral tongue and the floor of mouth arose based on anatomical considerations and provides a reasonable basis for comparisons. However, there is fairly little data to validate any classification system as a means of predicting outcomes or offering firm guidance to the surgeon. Independent of any defect classification, some authors have proposed goals for the reconstructive surgeon. Chepeha et al. described the ideal reconstruction of a hemiglossectomy defect as one in which the tongue fills the volume between the gums, teeth, and palate with the mouth closed; the reconstructed tongue can protrude to contact the premaxilla; the tongue is able to sweep the oral vestibule and protrude past the incisors; and maximal sensation is preserved in both the native and reconstructed surfaces of the tongue (Table 2.1). These goals can serve to direct the choices of the reconstructive surgeon. More recently, Chepeha et al. have begun the complex process of validating those goals and resulting techniques by comparing them to patient-reported measures of functional outcome.

Other efforts at describing functional outcomes have been reported as well. Lam and Samman performed a systematic review that included 21 reports describing a variety of techniques including free and pedicled flaps as well as primary closure. The authors identified resection of both the tongue tip and the floor of mouth as predictive of decline in speech intelligibility. Postoperative radiotherapy was the main predictor of diet limitations. There was no improvement in speech or swallowing function with free flap sensory nerve anastomosis, and there was no clear conclusion about the optimal reconstructive method based on swallowing or speech outcomes. Meta-analysis was not possible due to the heterogeneity of inclusion criteria, small sample sizes, and most importantly, the lack of a common vocabulary to describe the specifics of the reconstructive task and resultant functional outcomes.

Sensory innervation is possible for several vascularized flaps, including many flaps in common use. Studies of the effects of innervation are limited by many of the same factors that affect evaluation of other outcomes. A recent systematic review by Namin and Varvares provided a summary of the literature. Sensory innervation was associated with improved two-point discrimination and lower pressure sensitivity threshold. Biglioli et al. described better patient-reported outcomes related to speech and eating in sensate radial forearm free flaps. Yu and Robb in cohorts of patients undergoing anterolateral thigh (ALT) free flaps, reported better swallowing scores with innervated flaps but similar speech scores. Other studies have included a variety of objective measures of oral cavity function related to speech, chewing, and swallowing, but comparisons between innervated and noninnervated flaps have not shown innervation to provide a clear benefit.

The complex task of the reconstructive surgeon is made yet more complicated by delayed postoperative changes. The natural progression of all wounds involves ingrowth of myofibroblasts, which in turn bring about contracture. Linear scars shorten along their axis, and two-dimensional wounds shorten in two dimensions. The contracture of large-volume wounds results in substantial distortion of any nearby mobile tissue. Vascularized flaps contract the least, while secondary intention healing is associated with the greatest distortion. Noninnervated muscle will undergo atrophy over a period of 3 to 6 months. Because of that, free or pedicled muscle flaps are unsuitable for restoration of bulk. In contrast, vascularized fat is relatively stable over time, although some volume loss does occur with adjuvant therapy. This is the reason fasciocutaneous flaps are the first option of most surgeons for a reconstruction requiring restoration of volume. When selecting regional or free flaps, the surgeon must also consider donor site morbidity. Patients are owed ongoing critical appraisal to ensure that reconstruction brings about a minimal burden of functional and aesthetic deficits. Finally, the resources of the surgeon and the health care system should play some role in reconstructive decision making, as complex surgery requires specialized training and perioperative resources. Surgeons should understand the system in which the patient is treated in order to deliver successful and equitable care to a population.

2.5 Options for Reconstruction

2.5.1 Secondary Intention

Patient Selection

Allowing an oral defect to granulate can be an appropriate choice for selected defects. Intraoperative resource use is minimized. However, the time taken to complete epithelialization is longer as compared to other reconstructive methods. This may

Note

Sensory innervation has demonstrated an improved two-point discrimination and lower pressure sensitivity; however, comparisons between innervated and noninnervated flaps have not shown innervation to provide a clear functional benefit.
have impact on the timely initiation of adjuvant therapies (particularly radiation therapy) in patients with adverse pathologic features. Additionally, contraction of the healing wound is maximal with secondary intention healing and might be a major determinant of whether reconstructive goals are reached.

In the oral cavity, this wound contracture can result in tethering of the oral tongue to the floor of mouth or fixed gingiva. This is most true as the area of concern moves anteriorly and toward the ventral surface of the tongue. Consequently, secondary intention healing is most useful for small lesions at the lateral border of the tongue.

**Surgical Technique and Considerations**

The surgical site is left to heal. Note that secondary intention healing could be applied to a portion of an oncologic defect, with the remainder managed with primary closure or another technique as described below.

**Perioperative Management**

The expected course of wound healing should be discussed with the patient prior to surgery. Patients are encouraged to maintain meticulous hygiene during wound healing along with chlorhexidine rinses. Patients with large granulating intraoral wounds may experience bleeding, especially if they are taking anticoagulants or antiplatelet therapy.

**Pearls**

- Appropriate for selected small oncologic defects of the oral tongue.
- The effects of wound contraction are maximal.
- Time to complete healing may be prolonged.

**Note**

The main limitation of healing by secondary intention is the uncontrolled scar and contracture that can lead to tethering and a less than optimal functional recovery.

### 2.5.2 Primary Closure

Little data exist regarding the extent of tongue resection that warrants flap reconstruction. As previously stated in this chapter, the oral tongue’s primary function is to assist in bolus propulsion during swallowing as well as speech and articulation. Based on principles of replacing bulk and preventing tethering, flap reconstruction has become more prevalent in the literature and in practice. McConnel et al. performed a multi-institutional prospective study to assess the impact of primary closure, myocutaneous flap, and free flap reconstruction on speech and swallow. Patients who had less than 30% of their oral tongue resected and received primary closure fared better both in terms of speech intelligibility as well as subjective swallowing measures when compared to flap reconstruction. This suggests that primary closure in carefully selected patients can achieve optimal functional outcomes, as shown in Fig. 2.1.
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observation. They are started on a liquid diet which is advanced as tolerated.

Pearls
- Primary closure is best for defects that are limited to a single subsite.
- A combination of primary closure and secondary intention healing can be used for defects in which closure alone would lead to a tight closure or tethering.
- A small portion of the incision can be left open to allow egress of fluid/blood from the surgical bed.

2.5.3 Skin Grafts or Synthetic Allografts

Skin grafts have been used successfully for decades for defects of the head and neck, with relatively good success. They provide a thin, pliable tissue to be used in relining the oral cavity. Split-thickness skin grafts are known to have significant contracture and therefore should be used cautiously when reconstructing the tongue and the floor of mouth. Advancements in reconstructive techniques have allowed for more selective use.

More recently, acellular dermis has become a popular choice for intraoral grafting in lieu of a skin graft. It is a biologically inert dermal matrix that studies suggest can have equivalent take to skin grafts, and is more cost-effective than skin grafting while avoiding donor site morbidity. Previous radiation therapy and thickness of acellular dermis appear to have impact on success of skin graft take and should be taken into consideration.

Note

Split-thickness skin grafts are known to have significant contracture and therefore should be used cautiously when reconstructing the tongue and the floor of mouth.

Patient Selection

Most often, skin grafts are used in scenarios where primary closure is likely to result in tethering, but the wound is otherwise deemed inadequate for flap reconstruction. This includes wounds with large surface area but of relatively low volume. Grafts require a vascular wound bed to provide nutrients during early phases of healing. Hemostasis is of utmost importance to prevent hematoma or seroma, which would prevent graft coaptation to the wound bed. Immobility is also critical, as a graft that lays on a mobile structure, such as the tongue, has a reduced chance of complete take. Grafts in the oral cavity often require bolster dressings to allow healing. The ideal patient has a thin defect that does not communicate into the neck after cancer ablation is complete.

Surgical Technique and Considerations

Split-thickness skin grafts are most commonly harvested from the thigh, although other locations including the abdomen and inner aspect of the upper arm are described. Thickness varies, but at our institution it is typically taken at 0.016 to 0.020 inches according to surgeon preference. It is critical to take measurements of the defect but overcorrect to account for future contracture.

The graft is inset into the defect with absorbable sutures and any redundancy trimmed at that time. We prefer “pie crust” the graft and place tacking sutures down to the wound bed to promote adherence of the graft to the wound bed. A xeroform gauze bolster is fashioned to the defect and secured using tie over sutures. If there is concern for airway obstruction, a tracheotomy should be considered.

The surgical technique for acellular dermal matrix is the same as that for skin grafts. Choice of thickness has been shown to correlate with take, and therefore we use thin grafts to optimize take. Similar precautions to avoid mobility and graft separation from the wound bed are taken.

Perioperative Management

The patient is kept on antibiotics for approximately 7 days while the bolster is in place. He or she is maintained on a liquid diet until the bolster is removed and then advanced as tolerated.

Postoperatively, a dressing is placed on the split-thickness donor site for 10 to 14 days. If there is leakage, the wound can be reinforced with additional dressings or a fine needle can be used to aspirate excess serosanguinous fluid. After 10 to 14 days, the dressing is removed and allowed to dry out.

Pearls
- The success of the graft depends on the ability of the bolster to prevent movement or separation from the wound bed.
- Antibiotic prophylaxis should continue until the bolster is removed.
- Evidence supports use of acellular dermis as providing better outcomes and lower cost than split-thickness skin graft.

2.5.4 Local Flaps

Locoregional flaps have long been used to reconstruct complex defects of the oral cavity that are deemed unsuitable for primary closure or skin graft. A variety of local skin and muscle flaps were described but carried significant donor site morbidities, and often required more than one stage. The last 25 years have brought about a resurgence in use of local tissues with particular attention paid to the facial artery system of flaps.

2.5.5 Submental Flap

The submental flap was first described in 1993 by Martin et al. for use in facial defects but has quickly become a versatile option in intraoral reconstruction due to its tissue characteristics and proximity to the site of defect. It is based on the submental branch of the facial artery. This artery courses along the mylohyoid before sending perforators to the skin near or through the anterior belly of digastric. Its venous drainage is the submental vein, which most commonly drains into the common facial vein and into the internal jugular system but may drain into the external or anterior jugular veins. A skin paddle measuring 7 × 18 cm has been described, but the maximal flap size depends primarily on patient-specific anatomy.
Controversies exist regarding its use in oral cancer and the potential for levels IA and IB metastases. However, the literature suggests no increase in locoregional recurrence when this flap is used.\textsuperscript{16}

**Patient Selection**

As always, use of physical examination and imaging is critical in selecting the most appropriate reconstruction. The submental flap is most commonly used for reconstruction of medium-sized defects of the oral cavity including hemiglossectomy and floor of mouth defects. An ideal patient has enough laxity of the submental skin that a flap harvest can be subsequently closed primarily without excess tension on the incision line. The need for a tracheotomy may potentially impact the ability to undermine the skin inferiorly and this needs to be considered. This flap is contraindicated in patients with known level I metastatic disease. Given the high rate of occult metastatic disease in oral cavity cancers requiring complex reconstruction, a meticulous dissection of the pedicle is imperative to assure no nodal tissue is left in the neck or transferred with the flap into the oral cavity. In addition, the use of this flap in men may be complicated by transfer of beard hair into the oral cavity which can be a nuisance and lead to hygiene issues (▶ Fig. 2.2). This problem is obviated by radiation therapy, which many patients require. If no radiation is given, the flap can be depilated via laser or other methods.

**Note**

Controversies exist regarding its use in oral cancer and the potential for levels IA and IB metastases. However, literature suggests no increase in locoregional recurrence when this flap is used.

**Surgical Technique and Considerations**

Prior to harvest, the defect size is quantified and a lenticular-shaped flap is designed in the submental region. A pinch test confirms the maximal width of flap that can be harvested. The length of flap harvested typically exceeds the measurement of the defect to allow for a closure that minimizes any standing cutaneous deformities.

The submental flap incision is incorporated into a standard neck dissection incision curving upward onto the underside of the mandible (▶ Fig. 2.3). The incision is placed anterior to the submental crease to assure capture of perforators arising near the anterior belly of the digastric. Handheld Doppler can be used to confirm presence of the submental artery and its perforators.

The superior skin flap is elevated to the mandible and the marginal mandibular branch of the facial nerve is identified and preserved. The incision is carried down to the mandible medially and the anterior belly of digastric is released from the mandible with care to preserve any identified perforators. The pedicle dissection begins proximally with identification of the facial vein as it arises from the internal or external jugular vein. The vein is traced proximal to distal until it passes under the anterior belly of digastric. Similar dissection is performed to identify and skeletonize the submental artery. Once the pedicle is confirmed, a distal-to-proximal dissection of the skin paddle can be performed. A sub- or supr platysmal dissection is carried from distal to proximal until the midline is approached. The dissection can then be deepened down to the level of the mylohyoid. Careful dissection is required as the flap is elevated off the mylohyoid to avoid disruption of the distal submental blood supply. Modifications such as described by Patel et al\textsuperscript{17} are performed on a case-by-case basis to incorporate mylohyoid muscle into the flap.

The pedicle is then further skeletonized, often to the takeoff of the facial vessels, to facilitate arc of rotation and ensure that lymphatics and nodes are excluded from the flap, as shown in ▶ Fig. 2.4. The flap can then be tunneled into the oral cavity and inset in standard fashion.

**Perioperative Management**

Patients are maintained NPO for 5 to 7 days and nasogastric tube feedings are initiated during this time. Perioperative antibiotics are given for 24 to 48 hours and consideration given to use of steroids based on concern for swelling. The flap is...
Reconstruction of the Oral Tongue and Floor of Mouth

2.5.6 Facial Artery Musculomucosal Flap

The facial artery musculomucosal (FAMM) flap was described in 1992 by Pribaz et al.¹⁸ as a versatile pedicled flap used to reconstruct an array of defects ranging from palatal clefts to floor of mouth defects. It is a thin, pliable flap composed of mucosa, submucosa, and a portion of the buccinator muscle. It is based on the distal facial artery and associated submucosal venous plexus. The artery courses just deep to the buccinator muscle and sends perforating branches to the overlying oral mucosa. It can be superiorly based or inferiorly based depending on the site to be reconstructed. The flap can be harvested as wide as 4 cm but is limited by the oral commissure, the Stensen duct orifice, as well as the ability to close the wound primarily. The length of flap is tailored to the defect but can be harvested up to 8 to 9 cm. The flap is typically interpolated over normal tissue and the pedicle is taken down at the second stage.

Surgical Technique and Considerations

For floor of mouth and tongue defects, the flap is inferiorly based. A handheld Doppler probe is used to trace the course of the artery beginning at the retromolar trigone and extending in an anterior oblique course toward the superior gingivolabial sulcus. The flap is incised down through buccinator, as shown in Fig. 2.5, and the facial artery is identified distally and ligated. The flap is then elevated distal to proximal in a plane just deep to the facial artery to avoid injuring facial nerve branches. The superior labial artery requires ligation. The flap is rotated into the defect and sutured with absorbable sutures. In the patient with an edentulous mandible, an incision can be made from the defect to the donor site and the proximal flap may be inset to facilitate a one-stage procedure. In dentate patients, a bite block may be worn for 3 weeks. However, in the authors’ practice, a different flap should be selected for dentate patients. A variation on this flap using the buccal artery, a branch of the transverse facial artery which supplies the buccinator from posteriorly, as in Fig. 2.6, has been shown possible for small-volume posterolateral tongue defects.²¹ The donor site is most often closed primarily, but use of the buccal fat pad can facilitate closure to avoid excess tension.

Perioperative Management

Patients are maintained NPO for 5 to 7 days and nasogastric tube feedings are initiated during this time. Perioperative antibiotics are given for 24 to 48 hours and consideration is given to use of steroids based on concern for swelling. The flap is evaluated for color and turgor to assure there is no compromise of the blood supply. Like with any flap reconstruction, a return to the operating room may be indicated in the setting of arterial or venous obstruction to rule out kinking or compression of the pedicle.

Pearls

- A handheld Doppler probe is useful to identify the course of the facial artery along the buccal mucosa.
- Careful handling of the flap is advised to avoid avulsion of the delicate perforators coming off of the facial artery.
- Inset should avoid kinking or twisting of the base of the flap.
2.5.7 Free Flaps
Advancements in locoregional flaps have dramatically augmented the choices available to the reconstructive surgeon. However, there is no debate that free flaps are superior in the reconstruction of complex three-dimensional defects, particularly when multiple subsites of the oral cavity are involved. There are also circumstances in which locoregional flaps are unavailable either due to prior surgery, radiation therapy, or patient anatomy. At our institution, the radial forearm and ALT flaps are the two most commonly selected free flaps for tongue defects, and remain the reconstructive options of choice for hemiglossectomy or larger defects.

2.5.8 Radial Forearm Free Flap
The radial forearm free flap was first described by Yang et al.\textsuperscript{22} in 1981 and popularized for head and neck reconstruction by Soutar and McGregor.\textsuperscript{23} It is the workhorse for oral cavity reconstruction due to its thin, pliable skin paddle, and long vascular pedicle. Its distance from the head and neck allows for a two-team approach, shortening the duration of surgery. It is based on the radial artery and its venae comitantes as well as the cephalic vein. A communicating vein is found between the superficial and deep systems that allows for a single venous anastomosis.\textsuperscript{24} The lateral antebrachial cutaneous nerve can be harvested along with the flap to create a sensate flap.

Patient Selection
When deciding on a radial forearm free flap, both defect-specific and donor site-specific considerations are important. This flap allows for large skin paddle that is thin and pliable, making it an ideal flap for reconstruction of tongue and floor of mouth. However, in most patients, the radial forearm has relatively thin skin and little adipose tissue, making it best suited for defects that do not require much bulk. When bulk is needed, additional fat from the forearm can be incorporated into the design and rolled under the flap in a “beaver tail” modification.\textsuperscript{25} Subtotal or total glossectomy defects will likely require use of a bulkier flap, such as the ALT flap.

Note
When bulk is needed, additional fat from the forearm can be incorporated into the design of a radial forearm free flap. The fat can be rolled under the flap in a “beaver tail” modification.

Understanding the vascular anatomy of the forearm and hand is also critical to successful harvest and limit the risk of hand ischemia. The radial artery most commonly takes off of the brachial artery approximately 2 cm below the antecubital fossa and enters the hand to become the deep palmar arch. The ulnar artery continues into the hand to become the superficial palmar arch which then interconnects with the deep arch. In patients who both have an incomplete superficial arch and lack communications between the two arches, sacrifice of the radial artery may lead to critical hand ischemia of the thumb and index finger.

An Allen test is routinely performed to assess perfusion of the hand with radial occlusion. At our institution, digital blood pressures in the thumb, index, and small fingers are measured preoperatively with radial and ulnar occlusion as an objective assessment of digital perfusion.

Surgical Technique and Considerations
After measurement of the oral defect, a skin paddle over the radial artery is designed. In cases in which the oral tongue and floor of mouth are involved, a bilobed design to separately reconstruct each subsite may help maintain mobility (see Fig. 2.7, Fig. 2.8).\textsuperscript{26} A template-based technique, as described by Chepeha et al.,\textsuperscript{2} is also commonly employed, as shown in Fig. 2.9 and Fig. 2.10. The cephalic vein is identified and ideally also captured by the skin paddle. Under tourniquet control, a lazy “S” incision is carried from the flap up to the antecubital fossa. Incisions are then made and subcutaneous flaps elevated just beneath the dermis to facilitate flap harvest. The length of the cephalic vein is then followed. Beginning on the ulnar side, the skin is raised in a suprafascial plane until the edge of the flexor
The carpi radialis tendon is identified. Dissection is carried over the tendon, preserving the paratenon. The fascia is then incised from distal to proximal, ligating branches of the pedicle that enter into the muscle. On the radial side, the cephalic vein is identified and raised with the flap. The superficial branches of the radial nerve are protected. Suprafascial dissection is continued until the brachioradialis tendon is reached. The fascia is incised from distal to proximal and any branches into the brachioradialis are ligated. The pedicle can then be ligated distally and flap elevated from distal to proximal. The communicating vein can be readily identified in most patients as a continuation of the radial vein into the cephalic system. The lateral antebrachial cutaneous nerve can also be seen as it enters the flap pedicle in the antecubital fossa. The flap is then reperfused for at least 15 minutes and hemostasis is achieved prior to harvest.

The flap pedicle is tunneled into the neck most commonly medial to the mandible and posterior to the mylohyoid. Partial flap inset is then performed with horizontal mattress absorbable sutures to achieve a watertight closure. The pedicle is then positioned in the neck to avoid kinking, twisting, or compression of the vessels. A microvascular anastomosis is performed under microscope or loupe magnification using 8–0 or 9–0 nylon. The authors routinely use a coupler device for the venous anastomosis (Fig. 2.11).

The donor site is closed using a split-thickness skin graft. The remainder of the incision is closed over a suction drain. A bolster or negative pressure system is applied to the grafted site followed by a volar splint with the wrist in slight extension and metacarpophalangeal joints in flexion.

**Perioperative Management**

All patients undergoing complex head and neck reconstruction receive 24 to 48 hours of perioperative antibiotics, with ampicillin–sulbactam being the preferred choice. The patient has a nasogastric feeding tube placed and is kept NPO for at least 7...
The ALT free flap was first described by Song et al.\(^29\) and popularized by Wei et al.\(^30\) among others. It is a versatile flap that can be raised as a fasciocutaneous or musculocutaneous flap and can be tailored to include added bulk as required by the defect. In the Western world, this flap often has significant adipose tissue and may be too bulky for partial glossectomy defects. It does play a significant role in the reconstruction of subtotal or total glossectomy defects as discussed later in this chapter.

The flap has a long vascular pedicle with a single artery and two venae comitantes that is most commonly based on the descending branch of the lateral circumflex femoral artery (LCFA). The flap is based on perforating vessels that most often run through the vastus lateralis muscle before piercing the fascia lata and entering the skin. Multiple variations have been described that can make for a less straightforward harvest than the radial forearm free flap.\(^31\) Perforators may arise from branches other than the descending branch of the LCFA. Should a thin flap be desired, the surgeon must dissect small myocutaneous perforators through vastus lateralis muscle. Donor site morbidity is quite low, but seromas occur with some frequency.

### Patient Selection

The ALT flap is best suited for medium-to-large defects of the oral tongue and floor of mouth that require addition bulk. Like the radial forearm free flap, it can be used as a fasciocutaneous flap to reconstruct more superficial defects. In many patients, the ALT may be too thick and may be variably thinned of subcutaneous fat to better fit the defect. For larger three-dimensional defects, it can be raised in conjunction with vastus lateralis muscle to fill in soft tissue deficits in the deep floor of mouth. It can be harvested with the lateral femoral cutaneous nerve as a sensate flap. There are few contraindications to harvest of this flap; however, flap harvest in patients with a history of severe peripheral vascular disease should be avoided as the LCFA may become an important collateral vessel in these patients.\(^32\)

Goals for reconstruction vary depending on whether the patient will have any functional tongue remaining. As described earlier, partial glossectomy reconstruction must focus on maintaining the mobility of the tongue to allow for proper bolus propulsion and articulation during speech (Fig. 2.12). Total glossectomy reconstruction requires a shift in philosophy, with primary focus placed on replacing bulk that allows for adequate neo tongue-to-palate contact and also allows for a safe swallow (Fig. 2.13). Patients with poor functional or pulmonary status preoperatively should be seriously considered for total laryngectomy so as to avoid life-threatening aspiration pneumonia.

### Surgical Technique and Considerations

Flap harvest begins with proper placement of the skin paddle. The flap is centered over a line drawn between the anterior superior iliac spine and the superolateral patella. A handheld Doppler probe is used to identify dominant perforators that are in highest concentration about the midpoint of the aforementioned line. There are additional perforators most often approximately 5 cm proximal and distal to the midpoint.\(^33\) After careful measurement of the oral cavity defect, a flap is designed about the dominant perforators in an elliptical fashion to facilitate primary closure.

The medial incision is then carried down through fascia lata and the rectus femoris muscle is identified based on its bipennate morphology—the chevron of the muscle fibers points superiorly. The fascia is then elevated off of the rectus femoris muscle and the search for perforators begin. In the rare situation, a septocutaneous perforator can be easily identified.
running in the septum between rectus femoris and vastus lateralis. More commonly, a close inspection of the underside of the fascia lata reveals a perforator entering into the flap from the vastus lateralis muscle.

Meticulous dissection is carried from distal to proximal through the vastus lateralis, unroofing the perforator until the pedicle is reached (▶ Fig. 2.14). This same technique is employed for any other perforators identified. A small cuff of muscle may be left surrounding the perforator to protect it during dissection (▶ Fig. 2.15). In the setting of a single perforator, the muscle may also alert the surgeon to twisting of the perforator. The pedicle can then be traced proximally and freed from the surrounding tissues. The nerve to vastus lateralis is identified and preserved, if possible. The limit of pedicle dissection is the branch to the rectus femoris (▶ Fig. 2.15), which should be preserved to avoid necrosis of this muscle. The lateral incision can then be made through fascia lata and the decision can be made to raise the flap as a fasciocutaneous flap or include variable amounts of vastus lateralis. The wound can be closed over one to two suction drains. Primary closure is possible with flap widths of 8 to 9 cm but may require skin grafting if a wider flap is necessary. Immobilization and weightbearing restriction are not required.

Free flap inset is then performed as described for radial forearm free flap and microvascular anastomosis is completed. In comparison to partial glossectomy which can commonly be
done via a transoral approach, total glossectomy commonly requires a mandibulectomy. Laryngeal suspension should be seriously considered in patients undergoing total glossectomy to help protect the airway and optimize swallowing outcomes.

**Perioperative Management**

All patients undergoing complex head and neck reconstruction receive 24 to 48 hours of perioperative antibiotics, with ampicillin–sulbactam being the preferred choice. A nasogastric feeding tube is placed and the patient is kept NPO for at least 7 days. Patients undergoing salvage surgery following radiation therapy are kept NPO for at least 14 days.

**Pearls**

- Meticulous dissection is required with myocutaneous perforators.
- If only one perforator is taken with the flap, some muscle left adherent to it can alert the surgeon to twisting during the inset.
- Aggressive thinning of ALT flaps has been described in order to optimize the reconstructed volume. Alternatively, an overly thick flap can be thinned secondarily, even after adjuvant therapy, and often under local anesthesia.
- During closure, the fascia lata is not reaproximated. The skin is undermined in the suprafascial plane to achieve a minimal tension closure.

**2.6 Adjuncts to Surgery**

Rehabilitation after oncologic surgery for tongue cancer begins with appropriate reconstructive surgery, but may continue afterward. The reconstructive surgeon should be aware of several adjunctive techniques from which some patients derive great benefit.

As with many patients undergoing treatment for upper aerodigestive tract cancers, a speech pathology consultation might be beneficial. Speech therapy, including a tailored program focusing on compensatory strengthening and adaptation, has been reported to result in improved speech outcomes.24

When the reconstructive aim of good palatal contact is not achieved, due to a combination of poor residual tongue mobility and inadequate volume, function might be improved by modification of the position of the palate. A prosthetist can fabricate a palatal drop prosthesis, in effect bringing the palate closer to the tongue. Speech function, particularly production of alveolar and palatal consonants, and swallowing, especially propulsion of food boluses, might thereby be improved. Some evidence supports speech and swallowing improvements with palatal drop prostheses.25 Outcomes may improve even further with a combination of a prosthesis and speech therapy.26

**References**


Reconstruction of the Oral Tongue and Floor of Mouth


3 Carcinoma of the Buccal Mucosa

Jason E. Thuener, Akina Tamaki, Andrew P. Stein, and Nicole M. Fowler

3.1 Introduction

Carcinoma of the buccal mucosa is less common than other oral cavity subsites in North America and western Europe, accounting for 5 to 10% of cases. However, the buccal cavity is one of the most common subsites in India, Taiwan, and Malaysia, reporting nearly 40% of oral cancers occurring in this subsite. The increased incidence is attributed to the prevalence of betel nut chewing in these areas. Most patients present in their sixth and seventh decade of life and there is a male predominance in most series. However, some series do report equal or higher rates in woman that are exposed to similar risk factors. Squamous cell carcinoma is the most common malignant lesion identified in the buccal cavity and is the main focus of the chapter. Other less common pathologies are discussed below.

3.2 Anatomy

The oral cavity is defined as the area extending from the vermillion border of the lips back to the junction of the hard and soft palate superiorly and the circumvallate papillae inferiorly. It is made up of eight subsites including lip, buccal mucosa, lower alveolar ridge, upper alveolar ridge, hard palate, anterior two-thirds of the tongue, floor of mouth, and the retromolar trigone (Fig. 3.1).

The buccal mucosa is composed of nonkeratinizing stratified squamous epithelium; however, keratinization can occur as a result of local trauma and in a variety of pathologic entities. Minor salivary glands are located in the submucosa all throughout the oral cavity and including the buccal mucosa.

3.3 Patterns of Tumor Spread

Squamous cell carcinoma of the head and neck spreads through direct extension, lymphatic metastasis, as well as extension along neurovascular bundles. True primary buccal mucosa lesions begin on the mucosa of the cheek between the alveolar ridges and anterior to the retromolar trigone. As these tumors progress, they can directly extend inferiorly into the mandible, superiorly into the maxilla and paranasal sinuses, posteriorly to the retromolar trigone, and toward the external skin (Fig. 3.3). It is at times difficult to know exactly where an oral cavity lesion started when they present at an advanced stage. As buccal cancer progresses to include other oral cavity subsites, the likelihood of locoregional spread increases and overall prognosis worsens. Buccal carcinoma may directly extend into the masticator space, a lymphatic-rich area. This finding is associated with a high rate of regional disease. Alternatively, spread may occur anteriorly to the floor of the mouth. This, as well as direct mandibular invasion, can provide access to neurovascular routes of spread along the trigeminal nerve. Lesions that extend out toward the external skin can directly involve the parotid gland and/or facial nerve. Metastatic lymphadenopathy from a buccal carcinoma will typically involve levels I and II first, before spreading to other levels of the neck (Fig. 3.4).
3.4 Pathology

Similar to other subsites of the head and neck, the vast majority of carcinomas of the buccal mucosa are squamous cell carcinomas. Other rare pathologies that have been described include malignant minor salivary gland tumors, sarcomas, mucosal melanomas, and lymphomas. The most common minor salivary gland tumors include adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma.

Premalignant and early squamous cell carcinoma of the buccal mucosa may present initially as leukoplakia, erythroplakia, or verrucous hyperplasia (Fig. 3.5). Persistent leukoplakia of the buccal mucosa should be excised as up to 20% will show pathology ranging from dysplasia to early squamous cell carcinoma. Erythroplakia in the oral cavity more commonly represents carcinoma in situ or invasive squamous cell carcinoma and should also be excised when persistent.

Special consideration should be made for patients with high-risk behaviors such as those who chew tobacco or betel nuts. Patients that regularly use betel nuts can develop oral
submucosal fibrosis which is associated with impaired oral function and the potential development of oral cavity carcinoma.

Verrucous carcinoma, a squamous cell carcinoma variant seen in the oral cavity and the larynx, most commonly presents on the buccal mucosa and the gingiva within the oral cavity.\(^6\) These slow-growing lesions are very exophytic with a papillary micronodular appearance. Histologically, they have a characteristic sharply circumscribed pushing margin that can be locally destructive. Although some case reports have described metastasis, this is very uncommon and may actually be due to incorrect pathologic diagnosis or small foci of invasive squamous cell carcinoma within the lesion.

### 3.5 Etiology

#### 3.5.1 Tobacco and Alcohol

Tobacco and alcohol are well-established independent and synergistic risk factors for the development of oral cavity carcinoma. They are the most preventable risk factors in oral cavity...
as well as other cancers of the upper aerodigestive tract. One review reported a threefold increased risk of developing an oral cavity cancer in smokers and a 10- to 15-fold increase with regular concomitant alcohol use. A fourfold increased risk of oral cancer has been reported in people who used smokeless tobacco when compared to nonusers. Associated risk also increases in a dose-dependent fashion.

3.5.2 Betel Quid

Betel quid is a combination of betel leaf, areca nut, and slaked lime. When combined with tobacco, it is called gutka. It is estimated that nearly 600 million people worldwide use some form of betel quid, predominantly within the Indian subcontinent and Asia. Precancerous lesions including leukoplakia, erythroplakia, and oral submucous fibrosis are commonly seen in betel quid users and accounts for the high incidence of oral cavity cancers in these geographic areas.

3.6 Staging

As described above, the buccal cavity is a subsite of the oral cavity. Tumor, node, metastasis (TNM) classification follows the same staging system for lip and oral cavity squamous cell carcinoma set forth by the American Joint Committee on Cancer (AJCC) (Table 3.1, Table 3.2). Clinical staging includes all information obtained on physical examination and imaging. Pathologic staging is possible after pathologic analysis of surgical specimens.

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm but not &gt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease:&lt;br&gt; Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face— that is, chin or nose (oral cavity). Tumor invades adjacent structures (e.g., through cortical bone) into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, skin of face</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease:&lt;br&gt; Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery</td>
</tr>
</tbody>
</table>

Note: The anterior border is the junction of the skin and vermilion border of the lip. The posterior border is formed by the junction of the hard and soft palates superiorly, the circumvallate papillae inferiorly, and the anterior tonsillar pillars laterally. The various sites within the oral cavity include the lip, gingival, hard palate, buccal mucosa, floor of the mouth, anterior two-thirds of tongue, and retromolar trigone. "Surface erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4.

3.7 Presentation

3.7.1 History

Initial presentation of buccal mucosa lesions can be extremely variable. Early-stage lesions may present as a nonhealing ulcer. Patients may complain of pain, bleeding, recurrent mucosal trauma, decreased oral intake, otalgia, and weight loss. As lesions become more advanced, they may complain of loose or painful dentition, numbness along the jaw or face, trismus, skin changes, and obstructive sialadenitis with parotid duct involvement. It is important to ask about risk factors including tobacco, alcohol, and betel quid. Any history of oral cavity lesions should be obtained. A full past medical history, comorbidities, and list of medications should also be obtained as this will impact certain diagnostic and therapeutic decisions.

3.7.2 Physical Examination

A thorough physical examination should be conducted to characterize the extent of the primary lesion as well as any cervical lymphadenopathy. When evaluating a patient with buccal carcinoma, special attention should be paid to the presence of trismus, loose dentition, parotid duct involvement, submucosal extension, facial numbness, facial paralysis, tongue mobility, and external skin changes. Involvement of adjacent subsites including the alveolar ridge, palate, retromolar trigone, floor of mouth, and tongue should be noted. Buccal lesions that abut the mandible need to be closely examined for evidence of periosteal or gross mandibular involvement. Advanced lesions may approach midline which may influence treatment planning and should be noted. The neck should be carefully palpated for any abnormal lymphadenopathy (> 1 cm and/or firm) with a focus on levels I to III. A mirror or flexible laryngoscope can be used to assess for synchronous primaries of the upper aerodigestive tract.

It is important to start considering the method of reconstruction at the initial presentation. This will be institution dependent and it is important to know the reconstructive surgeon's preference if a two-team approach is used at your institution. Skin laxity along the neck, chest, and shoulder should be assessed for regional flap options. Any prior neck incisions or scars should be noted. The presence of a pacemaker, medication port, or shunt may require consultation with other services if these will be in the surgical field. A thorough lower extremity

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Adjacent subsites</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node &gt; 3 cm but not &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>
exam, including pedal pulses, should be noted if considering anterolateral thigh or fibula flap reconstruction.

3.8 Diagnosis and Workup

History and physical examination will often give the practitioner a good sense of the extent of local disease. However, trismus and severe pain may limit a thorough examination in the office and an examination under anesthesia should be considered to obtain pathologic diagnosis, for tumor mapping and to appropriately counsel the patient on definitive surgical management. If the lesion is readily accessible, a biopsy should be obtained for tissue diagnosis in the office. If a tissue diagnosis has already been made, the original pathology should be obtained for review.

High-resolution CT scan of the neck with contrast should be obtained to fully characterize the extent of the primary lesion as well as any cervical lymphadenopathy. To help characterize buccal lesions, CT protocols such as breath holding, modified Valsalva, or puffed cheeks help elucidate the tumor mass by separating the buccal mucosa from the gingiva. CT scans of the neck typically include 2.5-mm cuts which is adequate in most situations. For posterior buccal lesions, special attention should be paid to the masticator space as well as the neurovascular bundles leading up to the skull base. Skull base foramina should be closely examined for very advanced lesions that approach the skull base, or in patients that present with facial numbness or facial paralysis. If a patient presents with advanced cranial neuropathies and skull base involvement is suspected, then MRI in addition to CT may be considered. Fig. 3.6 shows an example of a patient with recurrent buccal adenocarcinoma with maxillary perineural invasion (red arrow) that may have otherwise been missed on a CT scan. Mandibular invasion may be noted on CT as evidenced by cortical erosion near the primary tumor, peristomal reaction, pathologic fractures, or abnormal attenuation of the bone marrow.4

3.9 Treatment

3.9.1 Surgical Treatment

Primary Tumor

Primary surgical resection is the mainstay treatment recommendation for buccal carcinoma. Adjuvant treatment including chemotherapy and radiation (or combination chemoradiation) will be discussed below and are used for patients with advanced disease (stage III–IV) or those with adverse features. Involvement of the skull base, advanced cranial neuropathies, or encasement of the carotid artery may make a particular lesion technically unresectable, but this is uncommon.

In preparation for surgery, preoperative clearance should include an evaluation by anesthesia to allow for intubation planning. If the patient has trismus, mandibular involvement, or pathologic fracture, then it is recommended to have a discussion preoperatively with your anesthesiologist regarding the potential issues with masking or plans for awake fiberoptic intubation or tracheostomy. Also, requests for nasotracheal intubation will allow for the endotracheal tube to be out of the surgical field during the procedure if a tracheostomy will be unnecessary.

Transoral

Transoral resections are possible for smaller (T1/2), anteriorly located buccal cancers. The lips and cheek are retracted and a direct approach is used. About 5-mm margins should be drawn out circumferentially. The most common site for inadequate margins are deep, so care must be taken to ensure that an adequate deep margin is obtained. This may require resection of additional fat, buccinator muscle, or even facial skin, which is discussed later.

Cheek Flap

To allow greater exposure to the entire buccal space, a midline lip-split incision can be utilized. This should be considered in small posteriorly based cancers or in more advanced presentations. This incision can be made in one of three ways: (1) a staggered midline incision, (2) a chin-sparing (crescent-shaped circumventing the chin), or (3) a nonstaggered midline incision (Fig. 3.7). This incision is also continued inferiorly and connected with a standard neck dissection incision to allow wide exposure. Advantages of the chin flap are the wide exposure as well as maintenance of oral competence.
Transfacial

Advanced stage cancers with through and through cheek involvement will require resection of external cheek skin in addition to the intraoral buccal mucosa. In these cases, skin margins measuring at least 5 mm should be obtained circumferentially and direct access to the oral cavity is then utilized. The transfacial incisions can then be used alone or in conjunction with a midline lip and chin split or even a modified cheek flap by extending these incisions to the lip if a portion of the lips or oral commissure are involved.

Regardless of the approach, care must be taken with the parotid duct. This can be managed by identification and preservation if the primary lesion is located away from the duct. Alternatively, if the duct is at the edge of the resected margin, a sialodochoplasty may be performed. If the distal duct orifice is included in the resection, the duct may be traced and a more formal sialodochoplasty can still be performed if enough length is obtained. Finally, if there are no other options, the duct may require ligation which will usually be followed by a period of transient parotid obstruction and fibrosis before the parotid gland will inherently cease saliva production.

Marginal versus Segmental Mandibulectomy

Although there is general consensus that patients with mandibular invasion should undergo surgical resection, there is debate on the extent of mandibular excision that is needed. Segmental mandibulectomy (Fig. 3.8a) involves resection of a complete portion of the mandible leading to discontinuity while marginal mandibulectomy involves partial resection of the vertical height or sagittal diameter of the mandible.11 Previously it had been thought that lymphatic spread through the periosteum and bone was the mode of mandibular involvement as well as a
pathway into cervical nodes. Therefore, segmental resection was recommended in patients with squamous cell carcinoma adjacent to or invading into the mandible. Further research has shown that the mode of cancer spread to the mandible is through direct extension rather than lymphatic invasion. Segmental mandibulectomy can have significant functional and aesthetic consequences. This has led to exploration of more conservative options for mandibular preservation and partial resection of the mandible.

There is still ongoing debate on which patients would be appropriate for marginal mandibulectomy (> Fig. 3.8b) without compromising oncologic outcome. Management of the mandible in oral cavity cancer has largely focused on floor of mouth tumors abutting the mandible. Buccal cancers, including squamous cell carcinomas of the lower buccal sulcus, can also be intimately involved with the mandible. Numerous studies have shown comparable local control rates between marginal and segmental mandibulectomy in a select population of patients. Although still under debate, segmental mandibulectomy is indicated in advanced disease with bone invasion. An appropriate patient to consider for horizontal marginal mandibulectomy is someone who presents with a buccal mucosa primary located very inferiorly at the gingivobuccal sulcus. Those with more advanced primaries with clinical and radiographic evidence of invasion should undergo segmental mandibulectomy. If there is no clear clinical or radiographic evidence of mandibular involvement, intraoperative evaluation, including frozen pathology and gross inspection, needs to be used to determine if segmental, marginal, or any mandibulectomy is necessary. Marginal mandibulectomy is also not recommended in previously irradiated mandibles due to unpredictable pattern of cortical invasion compared to a nonirradiated mandible. It is also important to note that during marginal mandibulectomy, at least 10 mm of inferior bone should be preserved to minimize fracture risk.

Management of the Neck
Management of buccal carcinoma patients with neck disease at presentation is similar to other oral cavity subsites. An ipsilateral modified radical neck dissection (level I–IV) should be performed to treat the node-positive neck. An NO contralateral neck does not need to be electively treated in lateralized lesions. Treatment of the contralateral neck should be considered in very advanced lesions that approach midline, and involve multiple subsites.

In advanced buccal cancers there may be direct extension to the skin and perifacial nodes and so level I may need to be dissected in continuity with the primary tumor. Care should be taken to preserve the marginal mandibular nerve branches when able. Close assessment of this nerve’s function should be noted preoperatively and patients should be counseled if the marginal mandibular nerve will require resection.

Management of the NO neck in oral cavity cancers is complicated by the fact that approximately 10% of patients can have micrometastases at presentation. Therefore, traditional preoperative imaging and clinical evaluation may miss pathologically positive nodes. Observation of the NO neck is accepted practice if the risk of metastasis is less than 20%. Factors that increase the risk above 20% in buccal cavity carcinoma is not as well established as other oral cavity subsites. Jing et al did show an increased risk of cervical lymph node metastasis in any patient with a T3/T4 primary lesion as well as T1/T2 lesions with greater than 5.17-mm depth of invasion. Advanced carcinomas and early tumor with 4-mm depth of invasion or greater should be treated with a neck dissection because of the high risk of regional disease.

Recent literature studying the utility of sentinel lymph node biopsies for oral cavity cancer, including buccal subsites, has been emerging but have yet to change our standard practice regarding management of the neck. However, the use of serial sectioning in sentinel node biopsy may certainly catch a micrometastases that would otherwise be missed in traditional processing.

3.9.2 Radiation Therapy
Surgical resection is the standard of care for oral cavity cancer whenever possible. Radiotherapy alone can be considered in small T1 lesions of the buccal mucosa that does not involve the gingivobuccal sulcus. However, patients are then subjected to a risk of osteoradionecrosis and more limited options with locoregional recurrence. Brachytherapy is also an option for poor surgical candidates without involvement of the sulcus with local control rates of 80 to 90%, but treatment-related toxicity is fairly common. In general, radiation therapy is used as an adjuvant to surgery in the postoperative setting for patient with advanced stages III to IV disease or those with adverse features including positive margins, lymph node metastasis (with or without extracapsular spread), angiolymphatic invasion, or perineural invasion. Radiation therapy is usually given as a single fractionation daily, 5 to 6 days per week. There are additional treatment options of hyperfractionation that are not usually recommended if surgical resection with negative margins was achieved. Postoperative adjuvant doses usually average 60 to 65 Gy and are given over approximately 6 weeks.

3.9.3 Chemotherapy
Chemotherapy can be considered for definitive, induction, adjuvant, or palliative therapy. In buccal cancers, the primary mode of treatment is surgery and radiotherapy. Chemotherapy is often used as adjuvant therapy with radiation following surgical treatment. Multiple randomized trials have shown survival benefit with chemoradiation when compared with radiation alone in the setting of adjuvant and definitive treatment. Surgical resection followed by concurrent chemoradiation is recommended in T3/T4 lesions with adverse characteristics including extracapsular spread or positive surgical margins.

The most studied chemotherapeutic agents used in head and neck cancer include platinum compounds, taxanes, 5-fluorouracil, and methotrexate. Cisplatin was the first platinum agent shown to be effective in head and neck cancer treatment. Cisplatin is thought to cause DNA cross-linking, ultimately leading to cell death. Cisplatin remains the standard of care for head and neck squamous cell carcinomas, including buccal carcinomas. Combination therapies have been explored, but the majority of studies have not found a survival benefit with various combination regimens over conventional single-modality cisplatin. There are new molecular targets, which are under
clinical trial for treatment of head and neck squamous cell carcinoma. Cetuximab is an antibody against epidermal growth factor receptor that has shown promising response but yet to be the standard of care.\textsuperscript{23}

The efficacy of induction chemotherapy in oral cavity cancer is controversial. Induction chemotherapy can be followed by irradiation or concurrent chemoradiation, referred to as sequential therapy. A recent meta-analysis studying induction chemotherapy in oral cavity squamous cell carcinoma showed no significant improvement in survival but possible reduction in locoregional recurrence.\textsuperscript{24}

### 3.10 Complications of Treatment

Patients should be aware of both early- and late-onset toxicity related to radiation therapy. Dermatitis, mucositis, and xerostomia are the most common early-onset effects and they can develop around 2 to 3 weeks into treatment. Dermatitis can be exacerbated by sun exposure and the use of chemical irritants on the skin during treatment. Using lotions and ointments can also affect the depth of delivery and therefore alter the dose delivered to the skin. Mucositis can be a significant concern in buccal cavity cancer due to the location. The denuded epithelium can be significantly painful and nutritional status should be closely monitored. Chemotherapy can also contribute to mucositis, and when used in conjunction with radiation, severity can be increased. Xerostomia is a significant consideration in buccal cavity lesions due to the proximity of the buccal mucosa with salivary gland tissue. Unfortunately, xerostomia can be permanent when salivary gland tissue is included in the treatment field. One of the most dreaded late-term radiation therapy complications is mandibular osteoradionecrosis. This may result in chronic pain, pathologic fracture, chronic osteomyelitis, and the need for long-term antibiotics or even segmental mandibulectomy and reconstruction. Fig. 3.9 shows CT findings of mandibular osteoradionecrosis in a patient with history of an oral cavity cancer who was treated primarily with radiation.

### 3.11 Post-treatment Surveillance

Regular follow-up is essential after undergoing treatment for buccal cavity carcinoma to monitor for local recurrence, distant metastasis, second primaries, treatment sequelae, and early and late toxicities related to treatment. The National Comprehensive Cancer Network (NCCN) has published guidelines that give some direction when considering the frequency of follow-up after treatment and post-treatment imaging. The American Head and Neck Society (AHNS) recently published a review of these guidelines under the direction of their Education Committee.\textsuperscript{25} As always, patient-specific considerations will need to be taken into account with a multidisciplinary approach. Some of this will be guided by the extent of disease treated and the modality of treatment. It is important to remember that institutional and practitioner differences will influence the approach to posttreatment surveillance, especially in the absence of definitive recommendations. Speech therapy and nutrition have a crucial role during as well as immediately following treatment in patients who receive surgery and radiation. A thorough history and physical examination at each appointment is essential, and in many cases, the patient will pick up a recurrence before the practitioner. Concerning symptoms include persistent pain, otalgia, odynophagia, weight loss, new-onset ulcers, or new lymphadenopathy. Tobacco and alcohol cessation counseling should be addressed at each follow-up if the patient continues to use tobacco or drink. It is important to monitor remaining dentin after radiation and to recommend a formal evaluation as indicated. The practitioner should assess for signs of depression and also inquire about their support system. Obtaining baseline imaging of the primary and neck is best if performed around 12 weeks after treatment. In regard to buccal cavity carcinoma, this practice is most applicable to advanced-stage tumors that required surgery as well as adjuvant treatment as many other oncologic disciplines use imaging for surveillance. Early-stage lesions that were managed with surgery only can be followed with physical examination in the asymptomatic patient. Routine posttreatment chest imaging is recommended for patients aged 50 years or older with a 20 pack-year smoking history. Thyroid-stimulating hormone should be followed every 6 to 12 months in patients who received radiation.
3.12 Clinical Cases

3.12.1 Case 1

T4aN2bM0 squamous cell carcinoma of the right buccal mucosa.

Presentation and Diagnosis

This patient is a 59-year-old woman with a past medical history significant for hypertension, anxiety, depression, and smoking (60 pack-years) who initially presented with a several-month history of right facial pain, swelling, and right ear pain. She also noted a growing lesion on her right cheek.

On examination, the patient was noted to have a very extensive right buccal mucosal lesion that extended anteriorly to the oral commissure and laterally through the soft tissue and into the skin of the face (▶ Fig. 3.10). Neck examination was positive for palpable level I lymphadenopathy.

Workup and Staging

CT neck and PET/CT obtained preoperatively demonstrated the right buccal mucosal lesion as described previously as well as three to four necrotic, greater than 1 cm, lymph nodes in the right neck level I concerning for metastasis. At this time, patient was staged as a T4aN2bM0 squamous cell carcinoma of the right buccal mucosa. Triple endoscopy was subsequently performed under general anesthesia. No other lesions or masses were identified on direct laryngoscopy, bronchoscopy, or esophagoscopy other than the known right buccal mucosal mass.

Treatment Options

The recommended treatment options for this patient with advanced-stage oral cavity (buccal) squamous cell carcinoma would be multimodality. Options include surgical resection with postoperative adjuvant treatment based on pathologic features, or concurrent chemotherapy and radiation. This particular patient is at high risk for osteoradionecrosis and severe fibrosis of the buccal mucosa if chemotherapy and radiation are used for the primary treatment of the lesion. Treatment of the ipsilateral neck would also have to be completed given the suspicious lymph nodes.

Clinical Course and Outcome

The patient was discussed in our multidisciplinary tumor board and the decision was made to proceed with surgery and postoperative adjuvant treatment.

The patient underwent composite resection of the buccal lesion including excision of the oral commissure, skin/soft tissue of the face, right marginal mandibulectomy, and right neck dissection levels I to IV (▶ Fig. 3.11). The surgical defect was then repaired with a radial forearm fasciocutaneous free flap. Final pathology demonstrated invasive, moderately differentiated squamous cell carcinoma measuring 2.2 cm with lymphatic invasion, but without perineural invasion. Metastatic squamous cell carcinoma was present in five level I lymph nodes, with the largest one measuring 1.7 cm. There was no evidence of extracapsular extension. After recovering from surgery, the patient underwent radiation therapy to 64 Gy at 2.1 Gy per fraction using nine-field intensity-modulated radiation therapy (IMRT) technique. She also underwent concomitant postoperative chemotherapy with her radiation treatment. Posttreatment PET/CT demonstrated no further evidence of disease.

3.12.2 Case 2

T4aN0M0 squamous cell carcinoma of the left buccal mucosa.

Presentation and Diagnosis

This patient is a 53-year-old man with past medical history significant for hypertension, 45 pack-year smoking history, and significant alcohol use who initially presented with pain on the...
left side of his face for a few months, weight loss, left V3 paresthesia, and foul intraoral drainage. His pain was worse with eating and moving the jaw.

His initial physical examination demonstrated a large, indurated soft tissue mass arising from the left buccal space up to the zygoma, measuring approximately 10 cm long, 10 cm wide, and 4 cm thick. It extended down to the inferior border of the mandible, medially to the gumline of the first premolar and laterally to the parotid/masseteric spaces. Neck examination was clinically negative at that time for concerning lymphadenopathy.

**Workup and Staging**

CT neck was obtained that demonstrated an expansile, lytic-destructive process involving the body of the left mandible having large surrounding soft tissue lesion with areas of enhancement (Fig. 3.12). This lesion measured approximately 9 × 5.5 cm. There were also enlarged submental lymph nodes, largest measuring 18 mm in greatest dimension. Also, multiple enlarged left level II lymph nodes were present, once again, with the largest measuring 18 mm. CT chest was also obtained which was negative for any evidence of metastasis. Patient underwent triple endoscopy which was negative aside from the left buccal mucosal squamous cell carcinoma. Preoperatively, this patient was staged as having a T4aN2bM0 squamous cell carcinoma of the left buccal mucosa.

**Treatment Options**

The options for treatment for this patient with advanced-stage buccal squamous cell carcinoma once again would be multimodality. Similar to case #1, this patient would undergo primary surgery followed by postoperative adjuvant treatment to decrease the risk of locoregional recurrence. However, for a patient with unresectable disease or whose medical comorbidities preclude surgery, chemoradiation can be initiated for upfront treatment.

For this patient in particular, surgery would be favored due to the risk for pathologic fractures of the jaw, which can cause further morbidity to the patient. Therefore, the surgical approach for a patient with a tumor with such extensive bone involvement would include a composite resection of the involved buccal mucosa, segmental mandibulectomy, floor of mouth resection followed by reconstruction with an osteocutaneous flap.
free flap typically from the fibula, scapula, or radial forearm depending on the extent of the mandibulectomy. The recommended surgical treatment for the neck for this patient with suspicion for nodal disease on CT scan would be to at least proceed with a left selective neck dissection levels I to III. Level IV should be included with any suspicion of nodal metastasis at the time of the procedure.

**Clinical Course and Outcome**

The patient was discussed in our multidisciplinary tumor board and the decision was made to proceed with definitive surgery followed by adjuvant therapy. He was taken to the operating room and underwent left composite resection (buccal region, mandible, floor of mouth), left selective neck dissection levels IA to IV, left partial parotidectomy followed by reconstruction with an osteocutaneous fibular free flap (Fig. 3.13). Patient’s final pathology demonstrated an invasive, moderately differentiated squamous cell carcinoma of the buccal mucosa measuring 5.5 cm in greatest dimension and 4.5 cm in thickness. There was clear bone invasion but no evidence of angiolymphatic or perineural invasion. There were 40 total lymph nodes evaluated and all were negative for malignancy. Thus, patient’s pathologic stage was T4aN0M0. This patient underwent postoperative radiation therapy.

### 3.12.3 Case 3

T1N0M0 squamous cell carcinoma of the right buccal region.

**Presentation and Diagnosis**

This patient is a 74-year-old man with a past medical history significant for hypertension, hyperlipidemia, and prior alcohol/tobacco use (quit 30 years prior to presentation) who presented for evaluation of a recurrent right buccal mucosal lesion. Patient initially presented with concerns of a buccal lesion 1 year prior, and this was excised and pathology demonstrated carcinoma in situ. Subsequently, he developed a recurrence at this same site. Physical examination at that time demonstrated nodularity just anterior and lateral to the retromolar trigone at the level of the buccal sulcus on the right, with no evidence of bone involvement. Neck was negative for any clinically concerning adenopathy.

**Workup and Staging**

CT neck was obtained preoperatively, and it did not demonstrate any areas of specific concern or any adenopathy. The negative CT scan was not surprising in this clinical scenario, given the small size of the primary lesion as well as the history of excisional biopsy prior to the scan. Patient was staged as a T1N0M0 squamous cell carcinoma of the right buccal region. He underwent triple endoscopy which was negative for any further lesions aside from the known right buccal tumor.

**Treatment Options**

The treatment options for this patient with early-stage buccal squamous cell carcinoma would be primary surgery or definitive radiotherapy. In general, for a lesion that is surgically accessible, such as in this patient, surgery is the preferred treatment over radiotherapy. Indeed, in early-stage buccal squamous cell cancer, there is improved rate of locoregional control for surgery over radiation. However, a patient with significant comorbidities who cannot undergo surgery or a primary site in a difficult-to-access location could be treated with upfront radiotherapy. Patients with T1 lesions do not need to routinely undergo neck dissection or neck irradiation when the neck is clinically negative.

**Clinical Course and Outcome**

The patient was discussed in our multidisciplinary tumor board, and the decision was made to proceed with primary surgery with the goal for margin control. Patient underwent surgical excision (Fig. 3.14). His final pathology showed a tumor thickness of 1.5 mm and invasive squamous cell carcinoma less than 0.5 cm in greatest dimension. Thus, patient’s final
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pathologic stage was T1N0M0. Based on the early stage of this patient’s cancer, decision was made to follow closely as there were no adverse features such as perineural or perilymphatic invasion on final pathology. Patient has been closely followed over the past 3 years with no evidence of recurrent or new disease of the oral cavity.

References

4 Reconstruction of Buccal Defects

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4.1 Introduction

Defects involving the buccal subsite of the oral cavity arise from primary malignancies of the buccal mucosa or from malignancies from adjacent subsites that spread to the buccal mucosa. The buccal subunit plays a critical role in mastication, deglutition, speech, and oral competence. The overall goals of buccal reconstruction are to restore and maintain these critical functions. In this chapter, we present our approach to reconstruction of this subsite and discuss the most relevant reconstruction options for reconstruction of buccal defects.

4.2 Relevant Anatomy

The buccal mucosa consists of the mucosal lining of the oral cavity extending from the point of contact of the upper and lower lips anteriorly to the pterygomandibular raphe posteriorly. Superiorly, the buccal mucosa extends to the insertion to the mucosa of the maxillary alveolar ridge and inferiorly it extends to the insertion to the mucosa of the mandibular alveolar ridge. The buccal alveolar sulcus is at the junction of the alveolar mucosa and the buccal mucosa, and it provides a smooth gutter for secretions to be cleared. Maintaining this smooth gutter of the buccal alveolar sulcus is critical for optimal reconstruction of this subsite. As a result of its proximity to nearby subsites, reconstruction of the buccal mucosa also often involves reconstruction of adjacent subsites, such as the tonsil, palate, maxillary, or mandibular alveolus.

Lateral to the buccal mucosa is the buccinator muscle. The buccinator originates from the pterygomandibular raphe and inserts onto the modiolus. In addition to the pterygomandibular raphe, the buccinator also originates from the lateral surface of the maxillary and mandibular alveolus, which can be an important pathway of tumor spread in this subsite. The buccinator is innervated by the buccal branch of the facial nerve. The buccinator is a critical muscle of mastication as it maintains the food bolus in position when chewing. Lateral to the buccinator is the parotid duct and the buccal branches of the facial nerve. The parotid duct is typically intimately associated with the buccal branches of the facial nerve. The parotid duct pierces the buccinator and the buccal mucosa at the level of the second maxillary molar. Also on the superficial or lateral surface of the buccinator muscle is the buccal fat pad. The buccal fat pad is encapsulated in fascia and is supplied by the facial artery, superficial temporal artery, and terminal branches of the maxillary artery (Fig. 4.1).

4.3 Evaluation of the Buccal Defect

Reconstruction of buccal defects requires the critical evaluation of the following structures:

- Buccal mucosa.
- Buccinator and buccal fat pad.
- External cheek skin.
- Retromolar trigone and mandibular alveolus.
- Maxillary alveolus.
- Tonsil and soft palate.
- Oral commissure, upper and lower lip.

Buccal defects can be broadly categorized into the following:

- Buccal mucosa only.
- Buccal mucosa, buccinator, and buccal fat.

Fig. 4.1 The parotid duct pierces the buccinator and the buccal mucosa at the level of the second maxillary molar. Also on the superficial or lateral surface of the buccinator muscle is the buccal fat pad.
Reconstruction of Buccal Defects

- Buccal space with maxillary infrastructure or marginal mandibular defect.
- Buccal space with segmental mandible resection.
- Through-and-through buccal defect, soft tissue only.
- Through-and-through buccal defect, soft tissue and bone.

Any of these defects may also occur with involvement of the oral commissure, upper, and lower lip. With the mouth gently opened, the dimensions of the buccal mucosal defect are accurately obtained. It is important not to “oversize” the defect so that dead space is not created in which food and secretions may be trapped. If the defect extends beyond the buccal–alveolar sulcus, the ruler is folded in the sulcus and onto the maxillary or mandibular alveolus so that the sulcus is recreated with a fold incorporated into the flap. A tab for the alveolar defect is added to the measurement as needed on the superior or inferior aspect of the flap. If retromolar trigone, tonsil, or palate reconstruction is required, these subunits are measured and an additional tab is added to the posterior aspect of the flap, typically at a 45-degree angle.

Note
When designing a flap, it is important not to “oversize” the defect to avoid the creation of a dead space where food and secretions may be trapped. However, the natural buccal sulcus should be recreated to accommodate secretions and prevent oral incompetence.

4.4 Goals of Reconstruction

The primary goals of buccal reconstruction are as follows:
- Accurate volume and surface area reconstruction of the buccal space to maintain oral cavity obliteration and prevent trapping of secretions and saliva in the buccal space.
- Maintenance of smooth buccal–alveolar sulcus to maintain anterior to posterior movement of secretions.
- Restoration of facial contour and color match of surrounding facial skin in through-and-through defects.
- Restoration of the oral commissure with sensate tissue, maintenance of lower lip height, and suspension of the modiolus to optimize oral competence.

In considering the defect, the reconstructive donor site tissue, and the flap dimensions, it is ideal if the oral cavity defect is minimized upon closing the mouth. There should be no residual dead space; the goal is to enable the mucosal surfaces of the tongue and buccal reconstruction tissue to remain in contact when the mouth closed. The choice of donor site is critical so that the most appropriate tissue is used for the reconstruction to achieve an anatomical and functional buccal reconstruction. The volume of the reconstruction must be accurately assessed so that it accommodates the soft tissue defect. If the volume of the buccal space is not augmented during the reconstruction, trapping of secretions and food may occur. On the other hand, if excess volume is used to reconstruct this area, blunting of the buccal–alveolar sulcus may occur, making it difficult to maintain anterior-to-posterior directional flow of secretions, and the ability to achieve mouth closure may be affected. The measurement of the surface area of the defect is also critical in this regard, as reconstruction with a flap that is too large and flaccid for the defect can result in dead space in which food and secretions can be trapped. On the other hand, if the surface area of the reconstruction is inadequate, tethering of the buccal mucosa and decreased mouth opening, trismus, will occur.

4.5 Options for Microvascular Reconstruction

4.5.1 Radial Forearm

The radial forearm flap is a primary reconstructive option for reconstruction of intraoral soft tissue defects involving the buccal space (Fig. 4.2). These defects typically arise as a result of primary buccal malignancies, or from retromolar trigone malignancies extending to the buccal mucosa. The radial forearm flap can also be used to resurface defects that extend onto the mandibular and maxillary alveolus, retromolar trigone, tonsil, and, if necessary, the palate. The radial forearm donor site provides optimal reconstruction of most buccal defects except in the case of a through-and-through defect and defects with extensive bone involvement.

When using the radial forearm free flap, a preoperative Allen test is performed to ensure safety of a radial forearm harvest. A tourniquet may be used for the harvest, which is our preference. The measurements for the defect are transposed over the radial artery and designed so that the vessels exit the posterior aspect of the defect into the ipsilateral neck. A curvilinear incision is made in the proximal forearm through skin and adipose tissue and the skin flap is elevated laterally over the cephalic vein, which is dissected toward the hand and included in the flap harvest. The flap is then elevated from the radial aspect of the forearm to the medial edge of the brachioradialis, protecting the superficial branch of the radial nerve. This nerve can be found lateral to the brachioradialis tendon. The flap is then elevated from the ulnar aspect of the forearm to the lateral edge of the flexor carpi radialis. The pedicle is then dissected between the brachioradialis and flexor carpi radialis up to the radial recurrent artery. The vein comitantes may conjoin or send a tributary to the superficial venous system. The pedicle is ligated distally and deep branches to the radius are ligated, completing the harvest. A pedicled subcutaneous fat tab can be harvested from the brachial fat pad of the forearm and connected to the proximal edge of the flap. It can be rotated into the defect if more volume is needed.

Note
The radial forearm donor site provides optimal reconstruction of most buccal defects except in the case of through-and-through defects.

4.5.2 Lateral Arm

The lateral arm free flap is another reconstructive option for intraoral buccal defects. The lateral arm free flap is a fasciocutaneous free flap that is supplied by the posterior radial collateral...
artery. Similar to the radial forearm donor site, the lateral arm flap can provide reconstruction of the buccal mucosa, retromolar trigone, mandibular and maxillary alveolus, tonsil, and palate. Because it is thicker than the radial forearm donor site, it will provide greater volume reconstruction of the buccal space.

The lateral arm free flap and radial forearm free flap are used for similar defects: intraoral mucosal defects involving the buccal mucosa, retromolar trigone, mandibular/maxillary alveolus, tonsil, and palate. Compared to the radial forearm donor site, the lateral arm has a shorter pedicle and smaller diameter donor artery and venae comitantes, and thus for buccal reconstruction the authors prefer the radial forearm donor site. However, if the patient wishes to avoid the split-thickness skin graft on the distal forearm, the lateral arm donor site can be more conspicuous and hidden by a shirt sleeve. Furthermore, if the patient has a poor Allen test, the lateral arm free flap may be safely used (Fig. 4.3). Our technique for lateral arm harvest is described in Chapter 19.

**Note**

The lateral arm flap provides tissue that is thicker than the radial forearm donor site. Therefore, it is an excellent choice when greater volume is necessary of the reconstruction of the buccal space.

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**Fig. 4.2** (a) Patient with T3 N0 squamous cell carcinoma of the left buccal mucosa underwent resection of the buccal mucosa, buccinator, and buccal fat pad, preserving the cheek skin and subcutaneous tissue. (b) The resection extended to but did not include the lip. This defect was reconstructed with a radial forearm free tissue transfer, which, in this patient, was appropriate volume to maintain oral cavity obliteration without blunting the buccal–alveolar sulcus. If additional volume is needed, the brachial fat pad can be harvested and tailored to the volume of the defect. (c) A radial forearm free tissue transfer was used to reconstruct the buccal space, mandibular alveolus, and posterior floor of mouth. (d) The radial forearm provides pliable thin tissue that is an ideal donor site for the buccal defect. The radial forearm skin will contract and the design of the flap should take into consideration the contraction of the wound bed.
Reconstruction of Buccal Defects

4.5.3 Anterolateral Thigh

The anterolateral thigh (ALT) free flap is a useful donor site for buccal reconstruction, particularly for the through-and-through buccal defect. The ALT is most often a musculocutaneous flap, though 13% are supplied through septocutaneous perforators. Most often, the skin is supplied by the descending branch of the lateral femoral circumflex system, although it can also be supplied by oblique or transverse branches of the lateral femoral circumflex system. Because a large surface area can be harvested from the ALT donor site, through-and-through defects can be reconstructed by harvesting a large skin paddle and folding the flap to reconstruct the intraoral defect as well as the external skin defect.

For the through-and-through defect, the flap is designed so that the distal aspect of the ALT is folded intraorally to line the buccal mucosa. The most aspect of the flap is inset to the posterior edge of the defect. The distal thigh typically has a thinner layer of adipose compared to the proximal thigh. Inset of the flap proceeds intraorally from posterior to anterior. Once the intraoral defect is resurfaced, a small strip is then deepithelialized, and the proximal or superior aspect of the ALT is used to resurface the external cheek defect. The deepithelialized strip is then the anterior edge of the intraoral and external cheek defect. The proximal portion of the flap is then inset to the external cheek defect and the proximal or superior most portion of the flap can be trimmed to fit the defect. The donor site also allows access to the tensor fascia lata that may be used to suspend the oral commissure to the peristeum of the zygomatic arch. Our technique for harvest of the ALT is described in Chapter 19.

4.5.4 Fibula Osteocutaneous

The fibula osteocutaneous free flap is most commonly used for composite defects resulting from segmental mandibulectomy or infrastructure maxillectomy. These defects typically arise from resection of primary tumors involving the maxillary or mandibular alveolus that may spread beyond the buccal–alveolar sulcus onto the buccal mucosa (Fig. 4.4). Thus, when this donor site is used, the vascularized bone is used to reconstruct the lateral mandible or the infrastructure maxilla, and a wide skin paddle is harvested to resurface the alveolus, buccal–alveolar sulcus, and the buccal mucosa. Reconstruction of the midface and mandible is discussed in Chapters 6 and 10, respectively.

Landmarks for harvest of the fibula flap are the fibular head and the lateral malleolus. A line is drawn between these two points. The intermuscular septum is 1 cm behind this line and the axis of the septum shifts posteriorly as one travels inferior along this line. Septocutaneous perforators are typically located in the distal leg and the skin paddle is designed along the junction of the middle and distal one-third of the leg. Perforators can be identified using a Doppler. The anterior skin incision is made through skin, adipose, and the fascia overlying the peroneus longus. Once in the subfascial plane, the skin paddle is retracted posteriorly and the perforators are visualized. The peroneus longus and brevis are dissected off of the fibula and the anterior intermuscular septum is incised. The anterior tibial vessels are visualized and protected. The extensor hallucis longus is dissected off of the fibula and the interosseous membrane is incised. The posterior incision is then made down to the soleus fascia and the soleus is retracted posteriorly, exposing the flexor hallucis longus. Bone cuts are then made preserving 6 cm of bone proximal to the ankle and distal to the fibular head. The pedicle is identified deep to the posterior tibialis and pedicle dissection is completed, harvesting a small cuff of flexor hallucis longus along the perforators.

4.5.5 Scapular Osteocutaneous

The scapular osteocutaneous flap is an osteofasciocutaneous flap based on the circumflex scapular system. The skin paddle may be designed upon the transverse (scapular) or descending (parascapular) cutaneous branch of the circumflex scapular artery (CSA). The lateral scapular border, supplied by perforators of the CSA, may be harvested if bone is required for reconstruction. For buccal reconstruction, this donor site is typically reserved for large, through-and-through defects that also require mandibular or midface reconstruction with vascularized bone. The classic defect for this flap is the segmental mandibulectomy defect with through-and-through buccal resection (Fig. 4.5, Fig. 4.6). For these defects, the segmental mandibular defect and extensive soft tissue deficit can be reconstructed with a single flap, rather than a fibula free flap and a second soft tissue flap. The scapular flap provides several distinct advantages for the through-and-through defect. The subscapular system of flaps is the most versatile donor site available. The potential to harvest two separate bone grafts, the lateral scapular boarder and the scapular tip, provide the bone grafts necessary for complex bone defect such as the combine mandibular–maxillary defect. This system of flaps also provides the unique advantage of being available for reconstruction of the mandible and the maxilla.
Reconstruction of Buccal Defects

Fig. 4.4 (a) Dentulous patient with T4aN1 squamous cell carcinoma of the right mandibular alveolus extending onto the buccal mucosa, undergoing composite resection of the mandible, floor of mouth, and buccal subsites. Reconstruction of this defect completed with a fibula free tissue transfer using the fibula skin paddle to reconstruct the floor of mouth, alveolar, and buccal defect. (b) The fibular donor site provides the bone necessary to manage the mandibular defect and the thin skin paddle ideal for the buccal resurfacing. (c) The bone graft is plated into the defect and the vascular pedicle is transposed into the neck where the microvascular anastomosis can be performed.
Reconstruction of Buccal Defects

The advantage of three skin paddles, the scapular, the parascapular, and the latissimus dorsi. Finally, often under-recognized, the scapular skin paddle often provides an excellent color match for cheek reconstruction. In Fig. 4.7, long-term follow-up demonstrates that 2 years after a composite resection of a through-and-through cheek defect reconstructed with a scapular free flap maintains excellent skin color match.

**Note**

The scapular donor site provides the option of multiple skin paddles, two bone grafts, and an acceptable skin color match for through-and-through buccal–cheek defects.

The authors harvest this flap in the semilateral position using a beanbag for positioning. The parascapular skin paddle is preferred, but in large defects such as the through-and-through defect, the parascapular and scapular skin paddle can be designed so that the parascapular portion can resurface the external skin while the scapular portion reconstructs the intraoral defect. The triangular space between the teres major, teres minor, and long head of triceps is identified by palpation, approximately two-fifths down the lateral border of the scapula. The template of the skin paddle is centered over this triangular space and the lower 270 degrees are incised. The skin paddle is elevated from inferior to superior. The latissimus dorsi is identified as it extends over the inferior border of the scapula. The separation between the latissimus dorsi and teres major is...
identified. Retracting these muscles will expose the scapular tip and the angular branch from the thoracodorsal artery. Dissection proceeds from inferior to superior and the descending and transverse cutaneous branches of the CSA are identified superior to teres major, supplying the skin paddle. The superior incision is then completed, the teres minor is retracted superiorly and the long head of triceps is retracted laterally, and pedicle dissection is performed. The teres major is then cut off of the lateral edge of the scapula and the infraspinatus muscle is divided 3 cm from the lateral border. The lateral edge of the scapula is then harvested with a reciprocating saw, taking care not to injure the glenohumeral joint. Pedicle dissection is then completed into the axilla.

4.6 Options for Local and Regional Flaps

4.6.1 Buccal Fat Pad Flap

Small, superficial defects of the buccal mucosa may be reconstructed with a buccal fat pad flap. The buccal fat pad is supplied by the facial artery, superficial temporal artery, and terminal branches of the maxillary artery. The buccal fat pad is a well-demarcated concentration of fat surrounded by a fascial cleft that is located superficial to the buccinator, and anterior to the masseter muscle. The central portion of the buccal fat pad lies on the anterior surface of the masseter, with a superior...
extension between the masseter and temporalis muscles, and medially it may extend into the infratemporal fossa. It also has a buccal extension that extends inferior to the parotid duct toward the retromolar trigone. For buccal reconstruction, no additional incisions are required to use this flap as the resection bed will provide more than adequate access to the buccal fat pad. The buccal fat pad can be identified superficial (lateral) to the buccinators muscle and bluntly dissected and transposed into the defect. The buccal fat pad can then be covered with a split-thickness skin graft and a Xeroform gauze bolster can be sutured in place.

Note

The advantage of the buccal fat pad reconstruction is that no additional incisions are required to use this flap as the resection bed will provide more than adequate access to the buccal fat pad.

4.6.2 Submental Flap

The submental island flap is a regional soft tissue flap that is supplied by the submental branch of the facial artery. This flap may be used to reconstruct intraoral buccal defects with minimal bone component. Careful preservation of the submental vessels and perforators is required when using this donor site. Given that most buccal defects arise from primary buccal and adjacent oral cavity cancers, thorough dissection of the primary echelon lymph node basin in level I often precludes the use of this flap for buccal reconstruction. However, it may be used in patients with vessel-depleted necks, hypercoagulable state, or severe medical comorbidities. The authors’ harvest technique is described in Chapter 19.

4.6.3 Facial Artery Musculomucosal and Buccinator Myomucosal Flap

The facial artery musculomucosal flap has been described as a local flap option for intraoral reconstruction of select, small defects. This flap may be based inferiorly, supplied by the facial artery, or superiorly where it is supplied by the angular branch and/or branches of the infraorbital artery. Similarly, the buccinator myomucosal flap is an axial-pattern local flap based on the buccal or the facial artery. These local flaps have been described for reconstruction of small intraoral defects, but because the donor site intimately involves the buccal mucosa and buccinators, while most resections involving the buccal subsite will preclude the use of these local flaps, they may be applicable to select, small defects.

4.6.4 The Estlander Flap and Commissuroplasty

Buccal mucosal defects that extend to involve the oral commissure and upper or lower lip require careful reconstruction of the lip subunit. Preservation of oral competence is of utmost importance. To achieve oral competence in this setting, the goals of lip reconstruction in the setting of concomitant oral cavity reconstruction are to optimize sensate tissue forming the oral sphincter, recreate the labioalveolar sulcus, and maintain lower lip height. Neural preservation of the mental nerve and marginal mandibular nerve is critical; ipsilateral deficits in both of these nerves have significant functional consequences. In defects involving the oral commissure and the upper or lower lip, the Estlander cross-lip flap is used to reconstruct the oral commissure and up to 50% upper and lower lip defects. While blunting of the oral commissure and microstomia may result, maximizing sensate tissue of the oral sphincter is critical, and in our opinion, more important than anatomical reconstruction of the lip subunit with insensate tissue. If the oral commissure and equal amounts of the upper and lower lip are resected, the cut edges of the upper and lower lip can be carefully attached to recreate an intact oral commissure. After continuity of the flap is achieved, a split-thickness skin graft is sutured in place to cover the donor site. The initial reconstruction is full and oversized. The scapular skin paddle often provides an excellent color match for cheek reconstruction for more than 2 years after surgery.
oral sphincter is restored, the defect can be measured for free tissue reconstruction.

4.7 Other Options

4.7.1 Primary Closure

Primary closure of buccal defects may be performed in select cases. Typically, these are small (less than 2 cm) defects that involve the mucosa only. If primary closure is to be performed, one must ensure that mouth opening is not compromised and that the buccal–alveolar sulcus is maintained.

4.7.2 Skin Graft/Mucosal Graft

Skin grafts and mucosal grafts may be performed in select cases. However, skin grafts and mucosal grafts provide no volume and thus may only be considered in very superficial defects in order to maintain oral cavity obliteration. Skin grafts and mucosal grafts undergo significant contraction, which have significant functional consequences at the buccal subsite, resulting in reduced mouth opening. Thus, these are rarely used in buccal reconstruction.

**Note**

Skin grafts provide no volume and thus may only be considered in very superficial defects in order to maintain oral cavity obliteration. Additionally, skin grafts undergo contraction, which have significant functional consequences.

4.8 Conclusion

The primary goals of buccal reconstruction are to perform accurate volume and surface area reconstruction of the buccal mucosal defect to achieve the buccal–alveolar sulcus, restore facial contour, and to prioritize oral competence with sensate lip and oral commissure reconstruction. Reconstruction of the buccal subsite also often involves reconstruction of an adjacent subsite, such as the lip, alveolus, or tonsil. A careful, stepwise approach to evaluation of the defect as well as choice of donor site leads to optimal reconstructive outcomes. Choosing the correct donor site depends not only on the size of the defect and its location, but also on the patients' body habitus. The underlying principle that split-thickness skin grafts contract more than full-thickness grafts, and full-thickness grafts contract more than free tissue flaps, is an important guiding principle. The formidable challenges of buccal reconstruction are to achieve effective resurfacing of the defect that will not contract leading to trismus, yet not place an excessive flap that can result in tissue redundancy that will lead to food trapping.

References

5 Carcinoma of the Palate and Maxilla
Jamal Ahmed, Deepa Danan, Giovana Thomas, Jason M. Lebowitz, and Francisco J. Civantos

5.1 Introduction
Carcinomas involving the palate and maxilla mainly originate from primary oral cavity carcinoma. Although carcinomas may also originate from primary maxillary sinus carcinoma, extensive oropharyngeal carcinoma, and carcinomas of the orbit, infratemporal fossa, or facial soft tissues, this chapter focuses on the therapeutic considerations and ablative approaches for primary oral cavity carcinomas that involve only the oral hard palate and maxillary alveolar process.

5.2 Epidemiology
Carcinomas of the palate and maxillary alveolus are uncommon. As such, there are limited data available on malignancies in these subsites. While oral cavity cancers account for nearly half of tumors of the head and neck, tumors of the upper alveolar ridge and hard palate comprise only 5% of oral cavity malignancies. Hard palate tumors have a male-to-female ratio of 8:1.

5.3 Etiology
Tumors of the hard palate and upper alveolar ridge may be of epithelial (mucosal), salivary, hematopoietic, or mesenchymal origin. Unlike other regions in the head and neck, only about two-thirds of malignant neoplasms of the hard palate are squamous cell carcinomas (SCC). Limited data exist regarding tumors of this region. Because of the rich supply of minor salivary glands in the hard palate, salivary malignancies such as adenoid cystic carcinoma (ACC), adenocarcinoma, and mucoepidermoid carcinoma comprise a majority of the remaining portion of palatomaxillary tumors (Fig. 5.1). Other pathologies include mucosal melanoma, Kaposi’s sarcoma, and lymphoma.

Tobacco and alcohol are the primary causative factors in SCC of the oral cavity. Tobacco, either smoking or smokeless, is the major risk factor. Smokeless tobacco contains higher concentrations of nicotine and is present in the oral cavity for extended periods of time. Nicotine, while not a carcinogen, has cytotoxic effects and has been shown to enhance the effects of some carcinogens in the development of oral carcinoma in animal studies. Tobacco and alcohol have synergistic effects on carcinogenesis, possibly owing to the increased permeability of oral epithelium secondary to alcohol and the extended contact of tobacco products with oral mucosa. Reverse smoking, in which the lit end of the cigarette is placed in the mouth, is significantly associated with hard palate carcinoma. In South Asian countries, the habit of chewing betel quid is strongly associated with oral carcinoma and can produce field cancerization of the oral cavity. Several other factors, such as mechanical irritation from ill-fitting dentures, poor oral hygiene, and mouthwash have been suggested as etiologic factors in oral cavity SCC although this association is not definitive. The etiology of palatomaxillary tumors of salivary origin is unclear. Smoking and alcohol have not been shown to increase the risk of these malignancies.

Note
In addition to alcohol and tobacco, mechanical irritation from ill-fitting dentures, poor oral hygiene, and mouthwash have been suggested as etiologic factors in oral cavity squamous cell carcinoma.

5.4 Anatomy
The palate separates the oral cavity from the nasal cavity. The hard palate is bound anteriorly and laterally by the maxillary alveolar ridges and posteriorly by the soft palate. Invasion through the hard palate results in extension of tumor into the nasal cavity or maxillary sinus. The bony hard palate is composed of contributions from the maxillae anteriorly, and the palatine bone posteriorly.

The maxillae are paired bones that form the central structure of the midface, the upper dentition, the roof of the oral cavity, and the floor of the nasal cavity.

Fig. 5.1 Tumor of the hard palate, pathology consistent with low-grade neoplasm with myxoid stroma.
via the hard palate and upper gingiva, the floor and sidewalls of the anterior nasal cavity, and the floor of the orbit. Each maxilla provides structural support to the surrounding facial skeleton through a series of buttresses, which in turn determine the shape of the maxillary bone (▶ Fig. 5.2). These buttresses are composed of the four processes of the maxillary bone that extend from its central body: the frontal process, the alveolar process, the palatine process, and the zygomatic process. The alveolar process of the maxilla, paired with that of the opposite side, forms an arch in the axial plane that provides anterosuperior structural strength.

The frontal process of the medial maxillae extends superiorly on either side of the piriform aperture to articulate with the frontal bones, forming a buttress that provides vertical support and a strong connection to the cranial facial skeleton. Laterally, the zygomatic process of the maxillae articulates with the zygomatic bones, creating another axial arch structure which terminates posteriorly with the zygomatic process of the temporal bone, another anteroposterior buttress of force. Posteriorly, each maxilla articulates with the palatine bone. Within the oral cavity, the maxilla extends a palatine process, a flat shelf of bone in the axial plane that fuses in the midline with its opposite, forming the anterior bony hard palate. This shelf composes the concave roof of the oral cavity, and the convex floor of the nasal cavity. Anteriorly, there is a Y-shaped fusion line where the two bony maxillary shelves (the secondary palate) have fused with the premaxillae derived from the frontonasal process (the primary palate). Here, posterior to the incisors, a depression can be seen (the incisive foramen) which contains the exit points of the canals for the terminal branches of the nasopalatine nerves and the descending palatine arteries.

The other major bony contributions to the roof of the oral cavity are the palatine bones. Each palatine bone is “L” shaped in the coronal plane, with the shorter horizontal limb contributing to the bony palate posterior to the palatine processes of the maxillary bones. The superior aspect of the vertical limb of each palatine bone is marked by a notch, which in articulation with the sphenoid bone composes the sphenopalatine foramen. The sphenopalatine foramen communicates the nasal cavity medially with the pterygopalatine fossa laterally, and transmits the sphenopalatine artery. The pterygopalatine fossa is the superomedial-most aspect of the pterygomaxillary fissure, the space between the back wall of the maxilla anteriorly, and the pterygoid process of the sphenoid bone posteriorly. The vertically oriented pterygomaxillary fissure is continuous with the horizontally oriented inferior orbital fissure, into which the infraorbital nerve (of V2) is transmitted into the floor of the orbit from the pterygopalatine fossa. The posterior (infratemporal) face of the maxilla is also marked by foramen for the entry of posterior superior alveolar nerves to the upper dentition. Laterally, the posterior face of the maxilla has a palpable rounded eminence, the maxillary tuberosity, which articulates with the palatine bone.

The upper alveolar ridge is composed of mucosa overlying the alveolar process of the maxilla, extending from the gingivobuccal sulcus laterally to the junction of the hard palate medially. The hard palate is covered by thick mucosa bound tightly to the underlying periosteum. The submucosa in the posterior half of the hard palate contains minor salivary glands. The mucosa is covered by keratinizing stratified squamous epithelium. The hard palate derives its blood supply from the greater palatine and superior alveolar arteries. The greater palatine
artery descends in the palatine canal with its accompanying nerve and emerges on the palate from the greater palatine foramen supplying the gingiva and the mucosa and glands of the hard palate. The venous drainage of the hard palate is to the internal jugular venous system via the pterygoid plexus.22

The innervation of the hard palate is supplied by the greater palatine nerves and the nasopalatine nerves, which are branches of the maxillary division of the trigeminal nerve. The greater palatine nerve descends through the greater palatine canal and emerges on the hard palate at the greater palatine foramen, traveling anteriorly in a groove in the hard palate almost to the incisor teeth. It supplies the gums, the mucous membrane, and glands of the hard palate. Parasympathetic postganglionic fibers from the pterygopalatine ganglion also run with the nerves to supply the palatine mucous glands. The nasopalatine nerves enter the palate at the incisive foramen and supply the anterior portion of the hard palate.18 Tumor spread via perineural invasion may sometimes be detected by radiographic enlargement of the palatine foramina or widening of the palatine canals or foramen rotundum.21

Within the sinonasal cavities, the maxillary bone and palatine bones compose the floor and lateral walls of the nasal cavity. The body of the maxilla contains the maxillary sinus, the roof of which is the floor of the orbit. Within the roof of the maxillary sinus is the infraorbital canal, containing the infraorbital neurovascular bundle running from posterior to anterior, to exit on the anterior face of the maxilla via the infraorbital foramen. The maxillary sinus is lined by ciliated respiratory epithelium that propels mucous toward a natural ostium situated superiorly on the posterior medial wall of the sinus. Thus, any functional antrostomy must incorporate the natural to prevent recirculation of mucous.

### 5.4.1 Patterns of Spread

Anatomical pathways permit carcinoma of the maxillary alveolus and palate to spread to other areas. Posteriorly, the palatine canals connect the palate to the pterygopalatine fossa (Fig. 5.3). Anteriorly, the incisive foramina transmit the nasopalatine nerves and may be a route of carcinoma spread. The infraorbital nerve can allow carcinoma to spread from the facial soft tissues into pterygopalatine fossa. The pterygopalatine fossa is the medial and superior aspect of the pterygomaxillary fissure, which is continuous laterally with the infratemporal fossa. Through bony and soft tissue invasion, palatomaxillary tumors can involve the orbit, nasal cavity, oropharynx, masticator space, facial soft tissues, and the infratemporal fossa.

### 5.4.2 Staging

Palatomaxillary carcinomas can be staged according to the American Joint Committee on Cancer (AJCC) staging protocol for SCC of the oral cavity. Tumor and nodal status for lip and oral cavity tumors are used for staging. TNM staging criteria for cancer of the lip and oral cavity, adapted from the 2010 AJCC, are shown in Table 1 and Table 2.23 Of note, updates from the prior edition of the AJCC guidelines include division of T4 lesions into T4a (moderately advanced local disease) and T4b (very advanced local disease), leading to the stratification of stage IV into stage IVA (moderately advanced local/regional disease), stage IVC (very advanced local/regional disease), and stage IVB (distant metastatic disease).24 Stage groupings are shown in Table 5.1 and Table 5.2.

### 5.4.3 Prognostic Factors

Survival from palatomaxillary carcinomas is dependent on the extent of local and regional tumor, the presence of distant metastases, and the pathologic subtype of the carcinoma. Earlier-stage tumors have better prognoses whether treated with radiation or surgery. Palatomaxillary T1 SCC have a 75% 5-year disease-free survival when treated surgically, whereas with T2 carcinomas this drops to 50%. Eskander et al retrospectively

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**Note**

Carcinoma of the palatomaxillary complex can spread through preformed pathways. A good example is that the infraorbital nerve can allow carcinoma to spread from the facial soft tissues into pterygopalatine fossa.
Table 5.1 Staging of oral cavity squamous cell carcinoma

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm but not &gt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Moderately advanced local disease&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face—that is, chin or nose (oral cavity). Tumor invades adjacent structures (e.g., through cortical bone, into deep extrinsic muscle of tongue) (genioglossus, hyoglossus, palatoglossus, and styloglossus, maxillary sinus, skin of face)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
<tr>
<td></td>
<td>Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery</td>
</tr>
</tbody>
</table>

<sup>a</sup>Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4.

Table 5.2 Palatomaxillary carcinoma is staged according to the AJCC oral cavity staging system

<table>
<thead>
<tr>
<th>Oral Cavity</th>
<th>Regional lymph node staging system</th>
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<tbody>
<tr>
<td></td>
<td>NX</td>
</tr>
<tr>
<td></td>
<td>N0</td>
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<tr>
<td></td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td>N2a</td>
</tr>
<tr>
<td></td>
<td>N2b</td>
</tr>
<tr>
<td></td>
<td>N2c</td>
</tr>
<tr>
<td></td>
<td>N3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Midline nodes are considered ipsilateral nodes.

examined 97 patients with advanced (clinically T3 and T4) SCC of the hard palate and maxillary alveolus treated surgically, and found a 3-year disease-free survival of 70%. A significant proportion of these patients (26%) were found to have occult metastases that can impact disease-free and overall survival if not adequately treated. Results of a retrospective analysis performed at Memorial Sloan Kettering Cancer Center, spanning 21 years with median follow-up of nearly 5 years, revealed that tumors of the hard palate and upper alveolus are associated with a high rate of regional failure, which results in poor survival, despite attempted salvage. This retrospective study included 139 consecutive patients with median follow-up of nearly 5 years. The authors reported a high incidence of regional failure. While few patients (8%) displayed clinical evidence of nodal metastasis at the time of initial presentation, there was a high incidence of regional recurrence (30%) in patients who were clinically node negative (N0). Altogether, 38% of patients developed cervical metastases at some point. Patients with pT2 to pT4 primary tumors were at the highest risk of regional recurrence. Of patients with pT4 primary tumors, 38% experienced neck failure, and 53% developed neck metastases at some point, either at presentation or at recurrence. Because of this study’s outcome, the authors recommended elective neck dissection for the majority of tumors of the hard palate and upper alveolus, with the possible exception of localized T1 tumors without bone invasion. In that study, metastatic nodes were most commonly found in levels I and II, and rarely in level V. In the elective setting, therefore, they recommended a selective neck dissection of levels I to III.<sup>25</sup>

Another study by Yang et al, and published in 2015, reported results of their retrospective study conducted from 2003 to 2012 in China. The 3- and 5-year survival rates of the 62 participants were 66.6 and 57.3%, respectively. Occult lymph node metastases of maxillary SCC in tumor stages T2 to T4 occurred in 20 to 40% of patients. Because of this finding, the authors recommend elective neck dissection for management of T2 to T4 SCCs in the maxillary gingiva and hard palate. In addition, they postulated that postoperative radiotherapy can improve the prognosis and decrease the recurrence of SCC posterior to the first premolar plane.<sup>26</sup>

5.4.4 Clinical Presentation

Clinical presentation of palatomaxillary tumors is dependent on the histopathologic diagnosis. SCC of the hard palate or maxillary alveolus tend to present as a painful, bleeding, ulcerative lesion. Patients may be asymptomatic in early stages. Mean age of presentation in Western countries is in the seventh decade; however, in certain parts of Asia, age of presentation may be almost a decade earlier.<sup>27</sup> Patients may present with loose teeth or ill-fitting dentures in edentulous patients.
Carcinoma of the Palate and Maxilla

Minor salivary gland tumors can manifest as submucosal lesions with a smooth, normal-appearing mucosal covering. Because of the distribution of minor salivary glands on the hard palate, minor salivary gland neoplasms rarely appear in the midline,28 or on the alveolus. Mucosal melanomas most commonly appear on the hard palate and gingiva, and may present as smooth, pigmented lesions. Oral malignant melanoma is usually seen in middle age persons, and acts aggressively.28 Kaposi’s sarcoma presents in patients with AIDS: about a third of patients with AIDS and Kaposi’s sarcoma have oral lesions, most commonly on the hard palate, and these appear as violaceous, red, or blue lesions.30,31 They may also appear as a submucosal fullness with overlying erythema. Necrotizing sialometaplasia is an ulcerative lesion hypothesized to result from infarction of salivary gland tissue.32 The resulting ulcer is painless, can be deep, and may mimic a SCC.

Note
Unlike SCC that typically presents with a mucosal ulcer, minor salivary gland tumors can manifest as submucosal lesions with a smooth, normal-appearing mucosal covering.

5.4.5 Differential Diagnosis

The presence of squamous mucosa, numerous minor salivary glands, and lymphoid tissue allow for a wide variety of benign and malignant pathology to present on the hard palate. The differential diagnosis for hard palate malignant tumors includes SCC, salivary gland malignancies, lymphomas, adenocarcinomas, melanomas, and sarcomas. Mesenchymal tumors such as fibromas, lipomas, schwannomas, neurofibromas, hemangiomas, and lymphangiomas may also present on the palate.28

A given patient may have risk factors and clinical features that are highly suggestive of SCC, but a wide differential diagnosis should be maintained, especially in the setting of an unclear diagnosis.33,34,35 Numerous case reports have demonstrated situations where a single palate lesion eventually was found to be multiple overlapping diseases, some in which a benign diagnosis appeared with a malignant process.36,37 In addition, malignant tumors of the hard palate can appear in young patients as well.38,39,40

Malignant salivary gland tumors include ACC, mucoepidermoid carcinoma, carcinoma ex-pleomorphic adenoma, myoepithelial carcinoma, polymorphic low-grade adenocarcinoma, basal cell adenocarcinoma, and acinic cell carcinoma.41 ACCs are composed of 8 to 15% of all palatal salivary neoplasms.42 ACCs have a propensity for perineural invasion, and may cause neuropathic-type pain.43,44,45 The solid subtype of ACC portends the worst prognosis, as does the presence of perineural invasion and advanced age.46,47,48 ACCs do not typically spread through the lymphatics, and most recurrences are in the form of distant metastases, most often the lung.49

Note
ACCs have a propensity for perineural invasion, and may cause neuropathic-type pain.

5.4.6 Diagnosis and Workup

A thorough history is obtained, including a detailed evolution of the lesion and its symptomatology. Review of symptoms should evaluate symptoms that may suggest perineural invasion (pain out of proportion to examination, numbness). Emphasis on exposures that may result in gingival or palatal lesions should be obtained, including smoking or smokeless tobacco products, betel quid, and other carcinomas. Patients with primary oral SCC are at high risk for a second primary squamous cell carcinoma of the upper aerodigestive tract or the lungs.

Physical examination includes a comprehensive head and neck examination. Careful oral examination is performed to delineate the extent of tumor and the subsites of the oral cavity involved. Involvement of the soft palate, tonsillar fossa, dentition, or retromolar trigone, and whether the tumor crosses the midline should be assessed. The nasal cavity and nasopharynx are examined closely for transpalatal or posterior spread. The presence of trismus should be assessed which may indicate involvement of the masticator space. Second primary tumors of the upper aerodigestive tract should also be surveyed. Cervical lymphadenopathy should be noted, although clinically occult nodal disease commonly occurs.30,51,52 Metastatic disease from palatomaxillary squamous cell carcinoma tend to drain to neck levels I, II, III.

Note
The presence of trismus may indicate involvement of the masticator space.

5.4.7 Imaging

Computed tomography (CT) scan with contrast should be obtained to characterize the tumor size, and the presence of bony invasion, pathologic lymphadenopathy. CT scans provide excellent bony detail, however, overlying dental artifact can obscure images (Fig. 5.5). Magnetic resonance imaging (MRI) provides excellent soft tissue detail. MRI with contrast should be obtained if there is high suspicion for perineural invasion (e.g., ACC), invasion of the orbit, or intracranial spread. MRI provides excellent soft tissue detail to determine the extent of tumor and retained secretions (Fig. 5.5). Positron emission tomography (PET) scan measures areas of increased metabolic activity and can be useful in characterizing primary tumor, nodal disease, or possible recurrent disease.53

Note
MRI provides excellent soft tissue detail and can help to elucidate the difference between tumor mass and retained secretions.

5.4.8 Biopsy

Biopsy must be obtained for proper diagnosis and treatment. Imaging must be obtained and reviewed prior to biopsy, to
prevent inadvertent biopsy of a vascular lesion. Minor salivary gland tumors can be submucosal, and may necessitate intraoperative biopsy. Biopsy of exophytic masses can usually be obtained at bedside or in the operating room as part of staging endoscopy. Care must be taken to obtain the biopsy in a correct manner to ensure diagnostic accuracy.\textsuperscript{54} Sampling error remains the main cause of inaccurate biopsies. Fine-needle aspiration cytology can be obtained.\textsuperscript{55}

### 5.4.9 Treatment

Survival in patients with cancer of the hard palate or maxillary alveolus is significantly influenced by tumor type, T-stage, and cervical nodal metastases. Goals of treatment for hard palate and alveolar ridge cancer aims at providing the highest chance of cure at first treatment and maintenance of quality of life. The main treatment modality for cancers of these areas is surgical resection with or without postoperative radiotherapy, depending on the tumor type and stage. Since SCC is the most common type of cancer of the palatomaxillary area, we focus on treatment and outcome of this tumor type in the current section.

For early-stage disease of SCC, surgical resection alone with or without postoperative radiotherapy may be curative. However, for successful treatment outcomes, it is necessary to acquire complete surgical resection and to secure adequate resection margins. Functional impairments after surgical resection, such as dental occlusion difficulties, impaired mastication, hyponasality, and nasal leakage are the major causes of decreased quality of life.

For locally advanced maxilla and palate cancer, a multimodality treatment approach is strongly recommended to improve the survival rate and quality of life of the patient. These treatments include radiation and postoperative radiation or chemoradiation. Indications for postoperative radiotherapy include stage III or IV disease according to the 2007 criteria of the AJCC, the presence of perineural invasion or lymphatic invasion, the depth of tumor invasion, or a close surgical margin. Nevertheless, in the advanced stages, tumor control and survival rate are still considered to be unsatisfactory, with a local control rate of 50 to 60% and a 5-year disease-specific survival rate of 30 to 50%.\textsuperscript{56}

#### Note

Locally advanced carcinoma of the maxilla and palate requires multimodality treatment because of the high risk of locoregional and distant recurrence.

### 5.5 Surgical Treatment

#### 5.5.1 Primary Tumor Resection

**Approaches and Considerations**

Depending on the extent of tumor invasion, several variations of bone resection may be performed. When early growth tumors with alveolar mucosal invasion are present with no evidence of bone invasion, mucoperiosteal resection is advocated.\textsuperscript{57} As these early tumors extend into the interdental...
alveolus, marginal resection is preferred since the risk for tumor spread is higher, and free margins are difficult to achieve otherwise.

Marginal resection of the maxillary alveolus is also recommended for tumors with clinical evidence of periosteal invasion and/or adhesion to the underlying bone, but without radiologic evidence of bone resorption (▶ Fig. 5.6). For more advanced alveolar ridge tumors with bone resorption or gross tumor invasion, an en bloc resection of bone is the method of choice. The length of bone resected will vary depending on the tumor size. Bony resection will create inferior or partial maxillectomy defects, which may cause varying degree of communication between oral cavity and the nasal/paranasal cavities. Advanced T-stage lesions will require segmental resection of the maxillary floor. Total maxillectomy is the surgical removal of one entire side of the maxilla, including the premaxilla, alveolar ridges, and hard palate (▶ Fig. 5.7).

Brown has classified surgical resections into four vertical and horizontal components that when combined make a score. Class 1: maxillectomy without an oroantral fistula; class 2: low maxillectomy (not including orbital floor or its contents); class 3: high maxillectomy (involving orbital contents); and class 4: radical maxillectomy (includes orbital exenteration). Classes 2 to 4 are complemented by adding the letter a, b, or c. The horizontal or palatal component is classified as follows: a, unilateral alveolar maxillectomy; b, bilateral alveolar maxillectomy; and c, total alveolar maxillary resection.58

These defects can result in small or large defects in the palate, and palatal insufficiency causing oronasal regurgitation and hypernasality. It is prudent to coordinate a patient’s postablative care with a prosthodontist when available, to allow for expeditious placement of obturators when needed. A prosthodontist with experience working with maxillectomy patients will be more comfortable removing temporary bolster and packing material and placing an obturator.

The size, location, and extent of the tumor will dictate ablative approaches. In patients with ACC or SCC with perineural involvement, the possibility of tracing perineural invasion of the infraorbital or palatine nerves to the level of the skull base to obtain negative margins should be considered. This may also be done to debulk tumor in anticipation of postoperative radiation.

Tumors confined to the oral palate can be removed via a transoral inferior maxillectomy. En bloc tumor resection with a soft tissue margin of 1 cm should be obtained, as should intraoperative frozen section pathology control of margins. Specimens should be clearly labeled to allow for further resections in the event of positive margins. Bone eroded by tumor or abutting mucosal disease should also be resected. Extensive bone resection without evidence of bony erosion may not be necessary in cases of mucoepidermoid carcinoma.59 Tumor resections are frequently extended to include the nearby gingiva and dentition. This can create a fistula with the maxillary sinus, and preoperative preparation for obturation is prudent. Posteriorly, tumor can approach the palatine foramen, with resultant
spread to the palatine canal and the pterygopalatine fossa. Bony resection in this area can produce brisk bleeding from the descending palatine arteries. In addition, stimulation of the trigemino-cardiac reflex can induce bradycardia and hypotension.

**Note**

Tumors of the posterior palate may extend into the palatine foramen and gain access to pterygopalatine fossa through the palatine canal.

For carcinoma involving the malar aspect of the maxilla, anterior approaches become necessary for a medial or total maxillectomy. A transoral approach can be combined with a sublabial mucosal incision to partially deglove the midface, giving access to the lower midface and piriform aperture. Midface degloving can also be combined with a subconjunctival incision to avoid facial incisions altogether. For access to the superior midface and the infraorbital canal, facial incisions can be utilized. The lateral rhinotomy approach allows for the scar to be camouflaged in the nasofacial and nasolabial grooves, and along the philtrum. Approximation of the vermilion border after lip incision is crucial for normal postoperative appearance. The Weber–Fergusson incision has been described with numerous modifications to extend surgical access to the infraorbital rim and orbit.

If the tumor extends into the maxillary or ethmoid sinuses, or significantly involves the anterior, lateral, or posterior bone of the bony maxilla, a total maxillectomy may be indicated. Pre-operative imaging, especially MRI, is useful in planning operative approaches.

**Note**

The facial incisions used to perform a maxillectomy are predicated on the extent of the tumor and the surgical approach.

Maxillectomy may also be performed as a salvage procedure for refractory or recurrent disease. Complications can include hemorrhage, oroantral fistula, osteoradionecrosis, mucositis, and trismus. Patients with head and neck squamous carcinoma may also develop secondary malignancies, recurrent or refractory disease, or distant metastases.

### 5.5.2 Treatment of the Neck

Treatment for cervical N0 patients depends on the treatment of the primary lesion and the general condition of the patient. There are three major treatment strategies: elective staging neck dissection, elective neck irradiation, and wait and see/observation. Generally, the elective staging neck dissection is performed in patients with oral cancer when the risk for clinically occult metastasis exceeds 15 to 20%.

Elective neck dissection of the hard palate and maxillary alveolus have comparable rates of regional metastases to other oral cavity subsites (about 25%). At presentation, clinically evident nodal metastases are rare. For T1 squamous carcinomas of the hard palate and alveolus, neck dissection may not be necessary. For tumors T2 and greater, elective neck dissection may be of some benefit. Studies employing watchful-waiting and close surveillance for T2 tumors show feasibility of this approach in selected groups of patients, but have not clearly demonstrated noninferiority. These cancers are often undertreated, with increased rates of regional recurrence in the neck. Regional cervical recurrences are associated with poorer prognosis, thus elective neck dissection should be strongly considered in these patients. The risk of occult metastases increases with T3 lesions, and is markedly increased in T4 lesions. Elective neck dissections for patients with T3 and T4 carcinomas of the palate and maxillary alveolus improve disease-free and overall survival.

**Note**

Regional cervical recurrences are associated with poor prognosis, thus elective neck dissection should strongly be considered in patients with advanced maxillary carcinoma.
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There is a paucity of information regarding the employment of bilateral versus only ipsilateral elective neck dissections for palate and maxillary carcinoma. Tumors of the hard palate and gingiva have drainage pathways to bilateral retropharyngeal lymphatics, as well as level IB and level IIA lymphatics. In one study by Ramalingam and Ebenezer, 24 patients with oral SCC of the maxillary region were treated with surgery and elective bilateral neck dissection. Only one patient on final pathology was found to have bilateral neck disease (4.1%). Advanced tumors that cross the midline may reasonably be at high risk of bilateral lymphatic spread, although further studies are needed to evaluate the benefit of bilateral neck dissections.

5.5.3 Radiation

Postoperative radiation therapy to the primary site is usually reserved for T3 and T4 primary cancer, positive margins, buccal extension, vascular or perineural invasion, and positive lymph node metastasis, especially extracapsular spread. Radiation consultation may begin 3 weeks after surgery as wounds begin to heal. In addition, patients with poor dental health should be referred for dental evaluation early to prevent delay of radiation secondary to required dental work. Postoperative radiation for cancer of the upper aerodigestive tract should ideally begin 6 weeks after surgery, and it appears to be most efficacious if it is completed with a minimal interruption. There have been no prospective phase III trials to compare primary surgery with primary radiotherapy for cancer of the oral cavity.

Note

The indications for postoperative radiation therapy to the primary site are usually reserved for T3 and T4 primary cancer, positive margins, buccal extension, vascular or perineural invasion, and/or positive lymph node metastasis.

5.5.4 Chemotherapy

Chemotherapy can be used as an adjunct to radiation. The presence of microscopic positive margins and/or extracapsular extension (ECE) is considered high-risk for recurrence. Two trials have examined the efficacy of adding chemotherapy to postoperative radiation therapy (PORT) in patients with oral cavity carcinoma. The addition of chemotherapy to PORT in these patients resulted in a 13% absolute reduction in locoregional relapse at 5 years in the European Organization for Research and Treatment of Cancer (EORTC) trial 22931 reported by Bernier et al. and a 10% absolute reduction at 2 years in the Radiation Therapy Oncology Group (RTOG) trial 9501 reported by Cooper et al.

Note

The addition of adjuvant chemotherapy in addition to external beam radiotherapy for advanced disease suggests a 10 to 13% absolute reduction in locoregional relapse at 5 years.

5.5.5 Posttreatment Surveillance

Patients should receive a comprehensive head and neck history and physical examination, including mirror and fiberoptic examination as needed. This is performed every 1 to 3 months during the first year after treatment, every 2 to 6 months in the second year, and every 4 to 8 months during years 3 to 5. After 5 years, this is performed yearly.

Posttreatment baseline imaging of the primary and neck is recommended within 6 months of treatment, and reimaging indicated for worrisome or equivocal signs/symptoms, smoking history, or if clinical examination is not possible. Chest imaging should be obtained as clinically indicated for patients with a smoking history. For patients who received radiation to the neck, a thyroid-stimulating hormone (TSH) should be checked every 6 to 12 months. Follow-up should be done with speech/hearing and swallow therapists as needed, and regular dental evaluation should be carried out. Patients should also be monitored for signs of depression.

5.6 Clinical Cases

5.6.1 Case 1

This is a 50-year-old woman with a history of systemic lupus erythematosus (SLE) and tobacco abuse (10 pack-years, quit 5 years ago) who presented to an outside surgeon with a soft tissue mass in the right premaxilla. Biopsy revealed SCC, and she was treated with partial anterior maxillectomy and placement of a skin graft. Postoperatively, she was noted to have persistent ulceration, and biopsy confirmed persistent SCC. Re-resection with negative margins was obtained. On follow-up CT imaging, she was noted to have irregular tissue within the right maxillary sinus (+ Fig. 5.9), and PET scan demonstrated 18F-fluorodeoxyglucose (FDG) avidity in this area, as well as in cervical lymphadenopathy, concerning for recurrence with regional spread.

5.6.2 Treatment Approach

This patient was determined to have T2N2cM0 stage IV SCC. After confirming outside pathology with our institution’s pathology department, the patient was taken for surgery. A bilateral inferior maxillectomy and bilateral neck dissection levels IIA to IV were performed. A Xeroform bolster was placed in the maxillectomy cavity. Negative margins were obtained, and bilateral nodal disease was found with extracapsular spread. The patient had an uneventful postoperative course and was discharged. She received an obturator prosthesis, and proceeded with chemotherapy and radiation.

At follow-up 13 months later, she was found to have a second SCC of the lung, which was treated with radiation. She is without local or distance evidence of disease at 18 months from her surgery.

5.6.3 Case 2

This is a 55-year old gentleman who suffered a trauma and was incidentally found to have a hard palate lesion, initially thought to be due to intubation trauma. On follow-up, imaging revealed
an enhancing mass on the posterior hard palate without bony erosion (Fig. 5.10). Biopsy revealed carcinoma with squamous features. No pathologic lymphadenopathy was identified.

Further immunohistochemical staining was positive for p63, p40, CK5/6, and CK7, and negative for RCA. This was determined to be a mucoepidermoid carcinoma. PET scan did not reveal any regional or distant uptake.

**5.6.4 Treatment Approach**

This patient was initially staged as T1N0M0 stage I disease. The patient was taken to the operating room and a right inferior maxillectomy was performed. Negative margins were obtained. A Xeroform bolster was applied to the maxillectomy cavity and secured.

The patient was tolerating clear liquids the next day and was discharged. The final pathology demonstrated polymorphic low-grade adenocarcinoma, and no further intervention was necessary. The patient received an obturator and continues to follow up with an orthodontist for adjustments.

**5.6.5 Case 3**

This is an 80-year old woman, nonsmoker, referred for newly diagnosed SCC of the left maxillary bone. She initially presented with oral pain, and was found to have a mass on her left gingiva.
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This was biopsied, and confirmed to be well-differentiated SCC. CT scan confirmed a lesion eroding through the floor of the left maxillary sinus (Fig. 5.11).

5.6.6 Treatment Approach

This patient was staged as having T3N0M0 stage III disease. The patient was taken to the operating room for resection. An exophytic mass was seen to involve the left alveolar ridge in the groove between the alveolar ridge and the buccal mucosa in the gingival buccal sulcus and above the retromolar trigone. She received a left maxillectomy, left neck dissection levels IIA, III, and IV, with resection of soft tissue for margins from the surrounding mucosa. Negative margins were obtained. A split-thickness skin graft was placed to cover the demucosalized soft tissue, and a Xeroform bolster was placed. The patient had an uneventful postoperative course and was discharged 2 days after admission. Final pathology demonstrated negative margins, no perineural or lymphovascular invasion, and no involvement of cervical lymph nodes. The patient was tolerating soft diet with mild trismus treated with stretching exercises, and had no evidence of disease at last follow-up.

5.7 Conclusion

Cancers of the hard palate and maxillary ridge can be treated successfully with surgery with or without postoperative adjuvant radiation therapy. Because of the high rate of regional recurrence in neck, even in N0 patients, elective neck dissection is recommended for all patients, except for localized T1 tumors without bony invasion. Adjuvant radiation therapy should be used for T3 and T4 tumors, buccal extension, positive margins, perineural spread, or multiple lymph node metastases. Most patients can expect satisfactory swallowing, speech, and rehabilitation.

References


Fig. 5.11 (a, b) CT scan confirmed a lesion eroding through the floor of the left maxillary sinus. The red arrows mark the tumor mass.


Carcinoma of the Palate and Maxilla


6 Reconstruction of the Palate and Maxilla

Neal D. Futran

6.1 Introduction

Loss of midfacial structures secondary to tumor removal or severe trauma has significant functional and cosmetic consequences. The variable loss of both soft tissue and/or bone leading to collapse of the lip, cheek, and periorbital soft tissues as well as palatal competence presents a challenging dilemma for reconstructive surgeons. In addition, eating and speech may be impaired. Common reconstructive goals include consistently obtaining a healed wound, restoring the palate with separation of the oral and sinonasal cavity, support of the orbit or fill in the orbital cavity in cases of exenteration, obliteration of a maxillary defect, restoring facial contours, and recreating a functional dentition (Table 6.1).1,2

Fabrication and placement of a maxillary prosthesis has been a traditional and reliable method to obturate maxillary defects.3,4 This restores the oral/nasal separation which is the fundamental factor necessary for speaking and swallowing. Dentition can be included for cosmesis and chewing. The surgical complexity and length of procedure is less with obturators as compared to tissue reconstruction. Nevertheless, prosthetic rehabilitation has significant shortcomings and patients may become dissatisfied for several reasons. Speech and swallowing require use of the device, and it requires frequent removal and cleaning for hygiene. This may be cumbersome and technically difficult, especially for the elderly or those left with monocular vision. Poor retention due to denture bulkiness, poor residual dentition (both quality and quantity), and poor or deficient retentive surfaces can create leakage and oronasal regurgitation. Although initial use of a prosthetic device does not preclude future tissue reconstruction, performing immediate reconstruction is technically easier than secondary procedures. Additionally, immediate reconstruction of large defects averts significant psychological and emotional distress due to disfigurement during a delay period.

Surgical management of these defects with a variety of pedicle autogenous tissues dates back to the 19th century. Local palatal flaps for small defects were described by von Langenbeck in 1862,5 and revisited by Guilane and Arena in 1977.6 The mid-20th century marked use of flaps such as nasal septum, tongue, cheek, upper lip, pharynx, turbinate, forehead, and cervical for smaller defects.7 These techniques were largely supplanted by pedicled myocutaneous flaps developed in the 1960s and 1970s.8,9 They accommodated larger defects by providing a sufficiently large volume of well-vascularized tissue, but often brought too much bulk and tended to be poorly pliable. Given the complex anatomy of the maxillectomy defect, this form of reconstruction fell short of ideal.

In the 1980s, development of microvascular anastomotic techniques allowed for free tissue transfers, yielding a tremendous breakthrough in the ability to reconstruct defects in a single stage without the limitations of reach and orientation of regional myocutaneous pedicled flaps. This technique allows a wide array of donor tissue types to be used, allowing the surgeon to customize the reconstruction to match the defect. The various nuances of soft tissue and osseous shape, bulk, and quality can be incorporated into the reconstructive plan. A variety of free tissue transfer donor sites have been described for maxillectomy defects, including radial forearm,10,11,12,13 rectus abdominis,14,15 fibula,16,17,18,19 scapular system,20,21,22,23 and iliac crest.24,25 Flap selection should be determined by a variety of factors. The amount, location, and quality of residual bone of the midface, dentition, and/or denture bearing alveolar arch largely determine whether a bone-containing flap is necessary. Coleman26 emphasized the importance of functional reconstruction when addressing defects of the midface and orbits. Ideally, skin, soft tissue, mucosa, and bone would be matched to the characteristics of the appropriate flap prior to undertaking the reconstructive procedure. Length of the vascular pedicle, thickness or thinness of the skin, muscle, and subcutaneous fat, the volume of the tissue available, the durability and thickness of the bone, and donor site morbidity are all important factors.

Table 6.1 The goals of palatomaxillary reconstructive surgery

<table>
<thead>
<tr>
<th>Achieve a healed wound</th>
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<tr>
<td>Restore the palate with separation of the oral and sinonasal cavity</td>
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<tr>
<td>Support the orbit or fill in the orbital cavity in case of exenteration</td>
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<tr>
<td>Obliterate the maxillary defect</td>
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<tr>
<td>Restore facial contour</td>
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<tr>
<td>Recreate functional dentition</td>
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When only the soft tissue of the palate is reconstructed, conventional dentures can provide functional dentition if adequate teeth and/or retentive surfaces are available to provide stability. In many cases, however, soft tissue reconstruction alone results in a flatter surface of maxillary arch than in the native condition. Blunted neoalveolar contours are created and there is also the loss of the gingival buccal sulcus and palatal arch depth. This results in a “trampoline-like” surface so that the reconstructed maxilla functions poorly to retain a denture.10,15 (> Fig. 6.1). If sufficient underlying bone is available, osseointegrated implants may overcome this problem, but reconstruction of a large composite defect with soft tissue is done at the expense of dental prosthetic rehabilitative options. Soft tissue...
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free flap reconstruction of the maxilla should be reserved for those patients who retain adequate dentition for mastication and/or those patients who do not desire the rigors of more complex reconstructive procedures.

Note
Soft tissue flaps can result in a blunted palatal and neoalveolar contour with a loss of the gingival buccal sulcus and palatal arch depth. This results in poor denture retention and a compromise in oral dental function.

Alternatively, bony reconstruction partly preserves the three-dimensional ridge and allows use of osseointegrated implants for functional dentition when adequate bone stock is replaced9, 18,27,28 (Fig. 6.2). No one single reconstructive technique has been described to achieve all goals of maxillary reconstruction. This chapter discusses methods and options to restore form and function of the palate and maxilla to maximize the return to optimal patient quality of life.

6.2 Relevant Anatomy

The maxilla functions as the structural support between the skull base and the occlusal plane, resisting and absorbing the forces of mastication, anchoring the dentition, separating the oral and nasal cavities, supporting the globe and the face and its mimetic musculature.

The soft tissues of the midface are supported by the maxilla, which aesthetically provides much of the facial appearance unique to each individual and serving as an icon for the whole person. Because of the disparate shapes and sizes of tumors affecting the maxilla and the complex surgical anatomy, the broad category of “maxillectomy” encompasses a group of diverse defects that range from a small oroantral or oronasal fistula to a large cavity, bounded by the tongue inferiorly and the anterior skull base superiorly. The zygoma provides the malar eminence critical for facial projection. The orbital floor provides support for the position of the globe. The alveolus is critical for dentition. These areas must be restored if lost as part of the resection. Tumors of the maxilla are rarely confined by the bony walls. Thus, resection of adjacent tissues in the velum, palate, midface, and orbits is commonly performed simultaneously (Fig. 6.3).
6.3 Evaluation of the Maxillary Defect and Determining the Options for Reconstruction

In the 1980s, as noted earlier, development of microvascular techniques allowed for free tissue transfers, yielding a tremendous improvement in the ability to reconstruct defects in a single stage without the limitations of positioning and flexibility imposed by regional pedicled flaps. These techniques allow a wide variety of donor tissue types to be used, permitting the surgeon to customize the reconstruction to match the defect. The various nuances of soft tissue and osseous shape, bulk, and quality can be incorporated into the reconstructive plan. Flap selection should be determined by a variety of factors. The amount, location, and quality of residual bone in the midface; the quality of the existing dentition; and/or denture bearing alveolar arch determine whether a bone-containing flap is necessary. Ideally, skin, soft tissue, mucosa, and bone needs would be matched to the characteristics of the appropriate flap prior to undertaking the reconstructive procedure. Length of the vascular pedicle; thickness or thinness of the skin, muscle, and subcutaneous fat; the volume of the tissue available; the durability and thickness of the bone; and donor site morbidity are all important factors that must be considered.

Free flaps with sufficient bone stock to support osseointegrated implantation include the fibula, iliac crest, and sometimes, the scapula. The radial forearm free flap (RFFF) may be harvested with a bony component but the length and width of the bone available limit its use to small anterior defects not requiring implantation.

6.4 Classification of the Maxillectomy Defect

A classification system that succinctly groups the wide array of possible tissue losses can potentially help to focus discussion, limit reconstructive options, and compare results. Attesting to the complexity of these anatomical defects, the medical literature contains several classification schemes, no one of which is universally accepted.

In one classification scheme, Brown et al describe the maxillectomy defect by independent vertical and horizontal component. The vertical dimension (class 1–4) designates the extent of unilateral involvement, with emphasis on the orbit. The addition of a letter (a–c) to vertical classes 2 to 4 qualifies the defect in relation to the horizontal aspect of the maxillectomy, which includes the amount of palate and alveolar ridge sacrificed. Thus, 10 possible designations characterize maxillectomy defects in this system. So organized, the vertical component tends to have greater influence on aesthetic results, while the horizontal component has much greater functional consequences. This classification system incorporates the inferior deficits (dental, masticatory, and articulatory) with the superior ones (aesthetic, sinonasal, and orbital support) well. Alternatively, Cordeiro, with both Santamaria and Disa, described a slightly different four-part classification scheme. A type 1 defect delineated a limited maxillectomy which included one or two walls of the maxilla excluding the palate. Type 2 defects, or subtotal maxillectomy, included resection of the maxillary arch, palate, anterior and lateral walls of the maxilla with preservation of the orbital floor. Type 3 defects similar to Brown’s group described a total maxillectomy which included resection of all six walls of the maxilla including the orbital floor. In type 3A, the orbital contents are preserved, while in type B, the orbital contents are exenterated. Type 4 defect was described as an orbitomaxillectomy and included resection of the orbital contents and the upper five walls of the maxilla with preservation of the palate. By using this classification system, these authors were able to assess the surface area/volume requirement, need for palatal closure, and need for orbital reconstruction. They developed an algorithm to determine the most optimal flap with which to reconstruct each particular defect. One major drawback to this classification scheme is the lack of attention paid to functional dental rehabilitation.

Triana et al evaluated 61 midfacial defects treated with microvascular free tissue flaps. The major classification groups were inferior partial maxillectomy defects and total maxillectomy defects. The former group was subtyped into the extent of palate lost, while the latter group was subgrouped depending on whether the orbit was exenterated and the degree of malar bone and zygomatic arch lost. With this classification scheme, the utilization of a bone-containing free-tissue transfer mainly depends on the amount of palate and alveolar arch lost as well as the integrity of the remaining dentition. Soft tissue concerns followed those as described by both Brown and Cordeiro.

Another variation on these schemes to assist in reconstructive decision making is The Mount Sinai Classification system. It is based on the size of the defect in both a horizontal and vertical plane. The criteria that were established are based on the biomechanical properties for obturator stability and retention. No one classification scheme has been embraced universally, but surgeons may be guided by them for reconstructive options. In general, as the defect involves the zygomatic body and orbital floor, the ability for an obturator to be successful decreases. Also, as the dental support is lost, particularly in the canine region and across the midline, the decision-making process is swayed toward primary tissue reconstruction.

Specific patient factors determining the reconstructive choice include age, comorbid medical conditions, performance status, manual dexterity, motivation, and family support. The biological behavior of the tumor, the ability to resect the tumor, and margin status also determine whether tissue or alloplastic...
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reconstruction should be pursued. It is critical to approach each patient with a team of ablative and reconstructive surgeons and a maxillofacial prosthodontist to optimize the outcome.34

Note
When defects involve the canine and cross the midline, dental support is compromised and the decision-making process favors primary tissue reconstruction.

6.5 Palate Defects

Small defects involving alveolar ridge, teeth, and surrounding mucosa may be covered with a local flap. Numerous techniques are available, including those from the cleft lip and palate literature.35,36,37 Among these, the palatal island flap stands out as a versatile and reliable local flap capable of covering defects up to 15 square cm.6,38 This flap is based on the greater palatine vessels can be elevated for up to 90% of the hard palate, and rotated up to 180 degrees based on a single pedicle. A clinical example demonstrates the process of reconstruction and long-term result.

Marshall et al13 reported on the use of the radial forearm flap for reconstruction of deep, central palatal defects. In this series of six cases, the radial forearm proved ideal given its potential to be contoured in restricted, hard-to-reach midfacial defects. This flap was also able to provide dual skin lining to both the nasal floor and the palate due its superior pliability. Supporting this concept, Genden et al in 2003 compared patient satisfaction between 10 cases of palatal reconstruction with the RFF and defect-matched patients rehabilitated with a prosthetic obturator. All the patients in both groups were able to resume an unrestricted diet with normal mastication and articulation. Both groups achieved equivalent satisfaction scores with regard to appearance, chewing, and taste; however, the patients reconstructed with an RFF reported higher satisfaction scores in speech, comfort, convenience, and social interaction.

6.6 Options for Reconstruction

6.6.1 The Palatal Island Flap

There are a variety of buccal mucosal and palatal flaps that have been described for the management of this defect; however, the palatal island flap represents an optimal option for isolated palatal defects. This flap is pliable enough to comfortably rotate into the defect, thin enough to assume the contour of the native palate, and because the palatal island flap is a mucoperiosteal flap, it provides a hearty partition that heals reliably to the adjacent palatal tissue (► Fig. 6.4a–c). In nonirradiated patients with small-to-moderate-sized isolated palatal defects, the palatal island mucoperiosteal flap is an excellent primary reconstructive option. The donor tissue based on a single greater palatine neurovascular pedicle can be rotated and safely transposed across the hard palate. The mucoperiosteum associated with the flap serves as a barrier to effectively separate the oral and nasal cavities. The secondary defect, which results from harvesting a palatal island flap, remucosalizes over a 3- to 4-week period; however, patients can be started on an oral diet between 2 and 4 days postoperatively (► Fig. 6.5a–d).

Palatal defects that do not cross the midline can be easily repaired using this single-stage local flap. Similarly, posterior palatal defects requiring resection of the maxillary tubercle and dentition posterior to the ipsilateral canine are also amenable to reconstruction using the palatal island flap. The mucosa remains sensate, which aids in mastication and oral transport and more importantly, coverage of this defect using the palatal island flap does not preclude the successful retention of a tissue-borne denture.

Surgical Technique and Considerations

- The blood supply of the palatal island flap is the greater palatine artery and vein. The neurovascular pedicle emerges from the palatine foramen before entering into soft tissue of the palatal mucosa.
- The posterior aspect of the palatine foramen is composed of a thin column of bone that can be fractured with a straight osteotome to release the neurovascular pedicle from the foramen and provide greater rotation of the flap if necessary.
- When designing the flap, it is important to carefully template the defect. The flap dimensions should be designed to closely match the defect to prevent redundancy. As the flap rotates into position, it will shorten the flap length between 10 and 30%, so it is important to account for this in the design of the flap.
- The flap is raised in the subperiosteal plane to prevent injury of the neurovascular bundle. The flap should be raised from anterior to posterior until the palatine foramen is identified. This will provide the optimal length and rotation of the flap.
- When rotating the flap into position, special attention should be addressed to preventing a kinking of the palatine vascular pedicle.
- Once rotated into the defect, the flap can be sutured into position with 2.0 Vicryl sutures. In some cases, small drill holes can be placed through the hard palate along the leading edge to secure the medial aspect of the flap.

Patient Selection and Perioperative Care

The donor site requires little care. Typically, the donor site is left to reepithelialize without a dressing. Patients can be started on a clear liquid diet for 2 days, followed by a pureed diet for 2 days, and then advanced to a soft diet for 4 weeks. Oral hygiene should include peroxide and water (50:50) rinses three times a day and after meals. Pain control is seldom an issue. The donor site defect is not usually painful and over the course of 4 to 6 weeks, the donor site will reepithelialize.

There are few contraindications to using the palatal island flap for this approach; however, it should not be used for patients younger than 5 years and those patients that have been previously radiated. Children younger than 5 years may suffer a disturbance in palatal growth. Radiated patients may fail to reepithelialize and, in rare cases, osteoradionecrosis may ensue.
The maxillofacial prosthodontist can make a simple prosthesis to cover the donor site that will improve patient comfort while healing.

6.6.2 The Radial Forearm Free Flap

The RFFF is an excellent option for extensive hard palate defects and hard palate defects that involve a limited portion of the alveolus. It is indicated when the defect is too extensive to allow for a palatal island flap reconstruction or when a palatal island flap is contraindicated. The radial forearm is thin and pliable, so it will conform to the natural contour of the native palate yet hardy enough to provide a reliable oronasal partition. Typically, patients are happy with the permanency of the reconstruction. Functionally, patients are able to eat and speak normally and for those who require a tissue-borne denture, the radial forearm does not hinder denture retention or stability (> Fig. 6.5).
Note

The radial forearm is thin and pliable, so it will conform to the natural contour of the native palate yet is hardy enough to provide a reliable oronasal partition.

For patients who seek an alternative to prosthetic rehabilitation, the fasciocutaneous RFFF offers an ideal source of donor tissue for the reconstruction of large palatal defects. The RFFF is designed such that the cutaneous paddle serves to reline the oral palatal surface and a fascial component is raised adjacent to the cutaneous paddle so that it can be folded to provide nasal lining. The pedicle can be passed through a subcutaneous tunnel superficial to the mandible or deep to the mandible to gain access to the facial vessels for the vascular anastomosis. In our experience, we find this method of reconstruction reliable and effective in achieving a permanent separation of the oral and maxillary cavities.
nasal cavities and has become our primary choice for reconstructing these select defects of the palate in patients who have no medical contraindications.

While large palatal defects can be successfully managed with a prosthetic obturator, the inconvenience associated with maintaining oronasal hygiene and the necessity of relying on a prosthesis for communication and eating can compromise a patient’s quality of life. Soft tissue reconstruction of these defects either with a local palatal flap, a submental island flap, or a fasciocutaneous RFFF offer patients a single-staged reconstruction that obviates the need for a palatal obturator without interfering with the use of a tissue-borne denture.

Surgical Technique and Considerations

- Once the margins have been assessed and the defect has been finalized, the donor vessels for the microvascular anastomosis should be isolated and a subcutaneous tunnel from the palatal defect to the donor vessels should be created. The donor vessels, which are commonly the transverse cervical artery and vein or the facial artery and vein, should be dissected and isolated.
- Although passing the vascular pedicle medial to the mandible is preferable, on occasion, a pathway lateral to the mandible may be used. In such cases, the marginal mandibular nerve should be identified and protected. Passing the vascular pedicle deep to the nerve will minimize the likelihood of nerve injury.
- If the vascular pedicle is too long, the facial vessels may not provide the ideal geometry. Redundancy of the vascular pedicle can lead to kinking and thrombosis and therefore the superior thyroid artery and external jugular vein, or the transverse cervical system may provide a better option. These sites allow the vascular pedicel to travel a straight path and decrease the potential for kinking and thrombosis.
- After the donor vessels have been isolated and the subcutaneous tunnel has been created, the RFFF skin paddle can be designed. Ideally, it should be designed using a template so that the skin paddle closely matches the defect. Redundancy of the skin paddle will only hinder the final result. The skin will be used to reline the palate, while the fascia opposite the skin will serve as lining for the floor of the nose.
- Before suturing the skin paddle into the palatal defect, the vascular pedicle of the flap should be thinned and excess fat should be trimmed to facilitate passing the vascular pedicle through the subcutaneous tunnel. The pedicle should then be passed through the subcutaneous tunnel and positioned adjacent to the donor vessels.
- The forearm skin paddle can be sutured into the palatal defect using 2.0 Vicryl suture. Once this is complete, the vascular anastomosis can be completed.
- A passive drain is left in the neck at the site of the microvascular anastomosis.

Patient Selection and Perioperative Care

Postoperatively, parenteral nutrition is administered through a nasogastric feeding tube for 5 days after which the patient is started on a liquid diet for 2 days, a puree diet for 2 days, and advanced-to-a soft diet for 2 days before beginning a regular diet. A nasal trumpet can be placed immediately postoperatively if there is concern of excessive stress on the palatal reconstruction. We restrict the patient from nose blowing and encourage mouth-open sneezing to prevent excessive stress on the suture line during the first 2 postoperative weeks.

In the early postoperative period, the patient may experience a serosanguineous nasal discharge and nasal obstruction. However, over the course of 8 weeks, the floor of the nose will epithelialize and the intranasal swelling will regress. As a result, the patient will develop an improved nasal airway. During the healing process, we advocate saline nasal douches 8 to 10 times per day for hygiene and to encourage healing.

Note

This flap should have sufficient pedicle length to reach the neck vessels without the need for vein grafts. A coronoidectomy can be done to limit the potential impingement of the flap vessels in the pterygomaxillary space.
6.6.3 The Inferior Maxillectomy

When the defect described above is enlarged to include an oroantral or oronasal fistula, sealing the oral cavity becomes paramount. Creating this seal with soft tissue reconstruction may improve the functional outcome even if a prosthesis is used by improving hygiene, increasing tolerance of an imperfect device fit, decreasing the size and weight of the obturator, and making permanent the oronasal separation. The pedicled temporalis flap with skin grafting may provide adequate coverage for a larger defect or when prior irradiation demands healthier tissue.39 This flap may be passed to the oral cavity by performing anterior and posterior osteotomies to the zygomatic arch and mobilizing it to its attachment on the coronoid process, but the reach into the oral cavity can be limited.

More reliably, a fasciocutaneous radial forearm free tissue transfer provides a more ideal solution to palate coverage for these defects. Futran and Villaret40 used the radial forearm flap for a series of anterior arch defects requiring thin, pliable tissue with minimal bulk. Improved restoration of the arch contour was achieved in four by incorporating radial bone. While the partial radius bone stock cannot withstand osseointegrated dental implantation, these patients maintained a regular diet with the use of conventional dentures. In addition, patients had near-normal speech and an acceptable aesthetic result without retraction of the upper lip.

Futran et al16 report the use of the fibula free flap in 27 patients with defects including the palate that was not amenable to the use of a conventional prosthesis. This group consisted of 12 unilateral inferior maxillectomies, 8 bilateral inferior maxillectomies, and 7 total maxillectomies with orbital preservation. The principal determination in the choice of this flap was the size of the palate defect. When a maxillofacial prosthodontist determined that insufficient prosthesis-retentive surfaces remained, the fibula flap was chosen for its ability to support osseointegrated implants’ minimal need for vein grafts. All but one flap survived, and four had wound complications managed successfully with local wound care. Eighteen patients had osseointegrated implants placed with the remaining patients’ implantation pending. Cosmesis among the inferior maxillectomy patients, rated by the surgeon, patient, and patient’s significant other, was excellent. Speech was intelligible over the telephone in all patients. Fourteen patients enjoyed a regular diet and the remaining 13 patients used soft diet. Alternatively, Granick et al used of the scapular osteocutaneous free flap for this type of defect with acceptable results.20

6.7 More Options for Reconstruction

6.7.1 Radial Forearm Flap

The osteocutaneous RFFF provides a limited amount cortical bone with a pliable skin paddle. While the bone graft is not ideal for mandibular reconstruction, it is well suited for small alveolar palatal defects. Although rare, occasionally an isolated anterior palatal defect may confront the reconstructive surgeon. Bony reconstruction of the anterior palatal arch with an osteocutaneous RFFF is often sufficient to provide the infrastructure necessary to support a tissue-borne or implant-borne denture.

Surgical Technique and Considerations

- Up to 30% of the radial bone can be harvested in a boat-shaped design with a vascularized skin paddle.
- The bone can be shaped with a series of osteotomies that can be fixed with miniplates or 25-gauge wire.

Patient Selection and Perioperative Care

Defects of the anterior maxilla that are greater than half the palatal area often require a substantial volume of bone that can be harvested from the scapular tip; however, defects less than half the palatal surface area require less bone. The radial forearm osteocutaneous donor site is ideal for this defect. Although the radial bone is not well suited for osseointegrated implants, bone grafts can be used to augment the radial bone for the retention of implants.

The most important aspect of the perioperative care is maintaining bone graft stability during the healing process. We keep patients on a liquid diet for 4 weeks to promote bone graft healing.

6.7.2 Fibula Free Flap

When the orbital rim is preserved, the orbit and the canthus are supported (Fig. 6.7). The focus of the reconstruction should be directed toward reestablishing the bony alveolus.

Fig. 6.7 The hemimaxillectomy defect with orbital rim preservation. This defect preserves the functional and cosmetic component of the orbital rim.
Any of the vascularized bone-containing free flaps can be used to reconstruct this defect; however, the vertical component of the defect is less crucial. The fibular donor site provides an excellent source of bone with ideal vascular pedicle length but fails to provide the bone necessary to address the maxillary face. This can be managed with either a vertically oriented scapular or iliac crest graft or mesh in combination with the fibular bone.

**Surgical Technique and Considerations**

- The optimal donor site for reconstruction of the hemimaxillectomy defect depends on the extent of the vertical defect. In those defects where the orbital rim and zygoma are preserved, the fibular, iliac, or scapular donor sites can be used. Because the fibular donor site provides the advantages of a two-team harvest and the potential for a long vascular pedicle, it is an excellent choice (> Fig. 6.8).
  - The fibula should be harvested from the donor leg that is contralateral to the maxillectomy defect to allow the skin paddle to be used to line the neopalate.
  - A template can be used to facilitate the design of the flap and identify the sites for osteotomies.
  - The fibula is harvested in a standard fashion with an ellipse of skin sufficient to reline the oral palate.
  - Following the harvest, the osteotomies can be completed and the excess bone can be trimmed.

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**Fig. 6.8** (a) A 32-year-old man 8 months after a severe midface trauma with osteomyelitis and bone necrosis refractory to antibiotic therapy and requiring maxillectomy. (b) Axial CT scan showing loss of midface bone. (c) Intraoral defect with exposed maxillary bone and granulation tissue. (d) Fibula free flap fashioned into the inferior maxilla and alveolus. (e) Inset of fibula bone. (f) Three-month postoperative view of the intraoral result.
The vascular pedicle can be lengthened by dissecting the pedicle and the adjacent periosteum off the excess bone. The bone graft can be fixed to the remnant medial maxilla and the free edge of the remnant zygoma. The skin paddle should be transposed into the palatal defect to reline the oral palate. The remainder of the skin paddle can be turned upward to reconstruct the lateral nasal wall defect. In those cases where there is a significant vertical defect, Vicryl mesh can be used to bridge the defect between the inferior maxillary defect and the inferior orbital rim. In cases where the nasolacrimal duct is involved in the resection, it is important to perform a dacryocystorhinostomy (DCR) by either marsupializing the lacrimal sac using 5.0 chromic suture or placing a silastic lacrimal stent for 6 weeks. Because the sac is usually exposed during the resection, we prefer the former approach.

Patient Selection and Perioperative Care

Following the reconstruction, we place a silastic nasal trumpet in the nasal vestibule on the side of the reconstruction. This helps to stent the nasal airway and guide healing. In nonradiated patients, we begin a liquid diet on day 5 and restrict the patient from chewing on the operated side for 6 weeks. In irradiated patients, we typically delay a liquid diet until day 7 to 10 depending on the tissue condition.

Note
Careful attention must be paid to where the flap pedicle passes through the tunnel into the neck. There must be adequate room to prevent kinking or twisting of the vessels which can lead to flap failure.

6.8 Total Maxillectomy with Orbital Preservation

In addition to the considerable task of restoring oral functions, reconstitution of an inferior orbital wall and zygoma becomes paramount. Without adequate support of the orbit, enophthalmos, hypophthalmos, and diplopia may result. The reconstructive task for this defect is therefore more technically challenging than when the orbital contents are also resected.

Initially, soft tissue volume requirements dictated refilling the midface contour. Shestak et al41 used the latissimus dorsi flap to obtain a sealed palate and achieve an aesthetically satisfactory recontouring of the face and cheek soft tissues. The rectus abdominis and anterolateral thigh free flaps demonstrate similar flap attributes and similar postoperative results.14,15 The inclusion of fascia or skin may limit the unpredictable atrophy (30–70%) associated with denervated muscle flaps. These soft
tissue reconstructions, however, do not address the maxillary bony skeleton, particularly the orbit, zygoma, and alveolus.

Cordeiro and co-authors utilized this technique for midfacial reconstruction in 46 patients. Out of 46 patients, 43 tolerated an unrestricted or soft diet. Only 15 out of 46 had a useable prosthesis, but the authors stated this was not considered a requisite to assist chewing function. This approach was also successfully used by Futran in eight patients who underwent cranial bone grafting to restore the zygomatic bone and orbital floor in addition to the rectus abdominis or latissimus dorsi myocutaneous free flap (▶ Fig. 6.8a–j).

Vascularized osteocutaneous free flaps have the advantage of being more infection resistant than nonvascularized bone-graft reconstructions, and better able to maintain bony volume. For total maxillectomy defects with orbital preservation, the subscapular system of flaps, while technically more complex, offers perhaps the greatest versatility in flap reconstruction.19–21 Replacement of the alveolar arch inferiorly with the lateral scapula (supplied by the circumflex scapular artery) and the orbital floor and rim with the scapular tip (supplied by the angular branch of the thoracodorsal artery) suits this reconstruction well. The thoracodorsal artery supplies the latissimus dorsi muscle, which may be harvested partially or completely for a wide range of soft tissue reconstructive needs. Furthermore, each of the two components of this flap may be rotated independently of each other. In the series by Triana et al., a variety of flaps based on the subscapular system of vessels were used to reconstruct maxillectomy defects in 10 patients. Dental and/or orbital restoration was able to be performed in four of these patients with the use of osseointegrated implants.

A major innovation for use of scapular angle osteomyogenous flap for reconstruction of maxillectomy defects has been popularized by Miles and Gilbert.22 This shape of this flap allows for horizontal orientation to restore the palate or vertical orientation to reconstruct the orbitozygomatic defect (▶ Fig. 6.9a,b). The attached muscle seals the palate. This technique also allows for a longer vascular pedicle minimizing the need for vein grafts as compared to the conventional scapula flap.

The scapular bone may not always be suitable for placement of osseointegrated implants. Further disadvantages in the use of the subscapular system include inability to harvest the flap simultaneously with the extirpative procedure, difficulty in orienting the bone to provide orbit, zygoma and alveolar reconstruction, and the relatively short pedicle length.

Similar to its use for inferior maxillectomy defects, multiple case studies have described the fibula flap with its excellent bone stock and the soft pliable skin paddle that can be used for either intraoral and/or cutaneous reconstruction.16–18 Futran et al.2 describe the use of vascularized fibular osteocutaneous free flaps in seven patients with total maxillectomies and orbital preservation. Superior and inferior bony support was accomplished but cosmesis was only considered fair because of flattening in the midface. In comparison, one patient in this series whose flap failed and ultimately a prosthesis was judged to have poor cosmesis. Osseointegrated implants were placed or planned in nearly all of this group. The fibula bone stock is more reliably implantable than the scapula. This represents an advantage of the fibula over the scapula for this defect, although cosmesis favors the scapula.

The iliac crest free flap provides an excellent bone source for palate and maxillary reconstruction. Brown23 presented three cases of reconstruction utilizing this flap and had favorable functional results. A single block can restore the alveolus, zygomatic prominence, and infraorbital rim. The disadvantages of using this flap for the maxilla are its potentially excessive bulk, limited soft tissue mobility in relationship to the bone and short
Reconstruction of the Palate and Maxilla

Pedicle length, and donor site morbidity. Genden et al.\(^2\) were able to achieve complete oro-dental rehabilitation in six patients using this flap for these extensive palatomaxillary defects.

### 6.8.1 Anterolateral Thigh, Rectus Abdominis, or Latissimus Dorsi Free Flap

**Surgical Technique and Considerations**

- Choice of flap is based on surgeon preference and body habitus as each can be sufficient to fill this defect (▶ Fig. 6.10).
- The anterolateral thigh flap has less potential complications and most ease of working in two teams.
- The flap is harvested in a standard fashion. Sufficient sutures should be placed to suspend the tissue in the maxillary cavity.
- Each of these flaps has a sufficient pedicle length to reach the neck without the need for vein grafts.
- For improved orbitozygomatic contour and support, cranial bone grafts and/or titanium mesh can be used and then enveloped with the flap.

**Patient Selection and Perioperative Care**

Standard wound and flap care is initiated. Oral alimentation begins with liquids on postoperative day 5. The donor site is managed in a standard fashion.

#### Note

Holes can be drilled in the residual maxilla so that the deep portion of flap can be directly fixated and maintain the position of the tissue. The defect should be overcorrected by as much as 30% as these flaps will have a degree of atrophy.

### 6.8.2 Fibula Free Flap

See above.

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**Fig. 6.10** (a) A CT scan of a 57-year-old woman with mucosal melanoma of the medial maxillary wall and maxillary sinus. (b) Cranial bone grafts used to recreate the orbital floor and zygoma of the maxillary defect. (c) Design of the rectus abdominis free flap. It would be deepithelialized into three segments: palate, nose, eye. (d) Rectus abdominis free flap. (e) Soft tissue inset of flap wrapped around the cranial bone grafts. (f) Three-week postoperative anterior facial view. (Continued)
6.8.3 Iliac Crest Myo-osseous Free Flap

Surgical Technique and Considerations

- The flap is harvested in a standard fashion.
- Typically, only the internal oblique muscle is used for palatal coverage and no skin paddle is taken.
- The ipsilateral hip is used where the vessel anastomoses will occur. This allows for proper orientation of the bone for fixation and minimal torsion on the soft tissue.
- A template of the maxillary bony defect should be made and transposed on the iliac bone to create the ideal shape.
- Miniplates are used to fixate the iliac crest to the remaining maxilla. Careful closure of the donor site is necessary, often with mesh to reconstruct the anterior abdominal wall to prevent hernia formation.
- The muscle is allowed to mucosalize in the mouth and no skin graft is needed.

Patient Selection and Perioperative Care

- Standard wound and flap care is initiated.
- Oral alimentation begins with liquids on postoperative day 5.
- The donor site is managed in a standard fashion.

Note

Careful attention must be paid to where the flap pedicle passes through the tunnel into the neck. There must be adequate room to prevent kinking or twisting of the vessels which can lead to flap failure. This flap pedicle is short and the surgeon must be prepared for the need for vein grafts.

6.8.4 Scapula Free Flap

The scapular donor site represents an option to reconstruct the maxillectomy defect. There are a variety of techniques that can be used depending upon the extent and position of the defect. The scapular tip or lateral border of the scapula can be oriented vertically to address the alveolus and the vertical component of the defect. Often the skin paddle associated with this donor site is thick and less than ideal to reline the palate. As a result, the teres muscle can be harvested and used to reline the palate. Because the teres muscle has no epithelium, it relies on the adjacent mucosa to mucosalize the palate which typically takes six to eight weeks to complete. The mucosalization process is less reliable in patients that have been previously radiated (Fig. 6.11, Fig. 6.12, Fig. 6.13, Fig. 6.14).

Surgical Technique and Considerations

- The scapular donor site provides an excellent alternative source of bone for restoration of the vertical component of the maxillectomy defect. The flap should be harvested with the teres muscle or a skin paddle to reline the palate (Fig. 6.15, Fig. 6.16, Fig. 6.17, Fig. 6.18).
- A vein graft may be necessary for the venous anastomosis; however, a thoracodorsal reverse flow technique can be used to lengthen the arterial pedicle.
- When harvesting the scapular bone, the osteotomies should be extended medially to harvest enough bone to reconstruct the vertical defect.
- Following the harvest, osteotomies should be performed to accommodate the nasal aperture and the orbital rim.
Reconstruction of the Palate and Maxilla

Fig. 6.11 A 64-year-old man with a neglected basal cell carcinoma of the midface.

Fig. 6.12 Surgical defect includes maxilla, buccal mucosa, upper and lower lips.

Fig. 6.13 Surgical specimen.

Fig. 6.14 Patient’s upper denture used as template to fashion the bone reconstruction.
Three-point fixation of the bone should be completed at the free edge of the medial maxillary defect, the free edge of the nasal defect, and the lateral zygoma free edge.

The teres minor muscle or skin paddle can be transposed into the oral cavity to reline the palate and the lateral nasal wall.

Patient Selection and Perioperative Care

The scapular donor site provides an excellent source of bone for the hemimaxillectomy defect with orbital rim resection. The challenge with this donor site is the thickness of the skin paddle. Depending on the body habitus of the patient, the skin paddle may be too thick to appropriately reline the palate. In such situations, we advocate using the teres muscle similar to the method described when using the internal oblique muscle for the iliac crest donor site. Although the scapular donor site cannot be harvested using a two-team approach, we find this donor site ideal for the maxillectomy defect with orbital rim resection.
6.8.5 Scapular Angle Free Flap

Surgical Technique and Considerations

- The flap is harvested in a standard fashion.
- The patient needs to be in a lateral position, otherwise it is difficult to work with a second team at the head.
- There is more room than a standard scapular flap.
- A skin island is usually not harvested with this flap and the surround muscle is used to fill the soft tissue defect and restore the palate.
- A skin graft is not necessary as the muscle will mucosalize in the oral cavity.
- Typically, only the horizontal or vertical component of the bony defect can be restored.
- Miniplates are used to fixate the scapula to the remaining maxilla.
- Careful closure of the donor site is necessary, but the residual muscle does not need to be fixed to the residual scapula.

Perioperative Management

Standard wound and flap care is initiated. Oral alimentation begins with liquids on postoperative day 5. The donor site is managed in a standard fashion.

6.8.6 Iliac Crest Free Flap with Internal Oblique Muscle

Surgical Technique and Considerations

See Fig. 6.19, Fig. 6.20, Fig. 6.21, Fig. 6.22, Fig. 6.23, Fig. 6.24, Fig. 6.25.

- The flap is harvested in a standard fashion.
- A small towel roll is placed under the hip to accentuate the iliac crest.
- The ipsilateral hip is used for proper vessel orientation. A skin island is not harvested with this flap and the internal oblique muscle is used to restore the palate.
A skin graft is not necessary as the muscle will mucosalize in the oral cavity.

A template of the maxillary defect is made and transferred to the iliac bone to create the proper bony shape and size.

Miniplates are used to fixate the scapula to the remaining maxilla.

Careful closure of the donor site is necessary to recreate the layers of the abdomen.

Surgical hernia mesh is often used to reduce the risk of hernia formation.

Perioperative Management

Standard wound and flap care is initiated. Oral alimentation begins with liquids on postoperative day 5. The donor site is managed in a standard fashion. Patients will need to ambulate with assistance (walker, cane) for 4 to 6 weeks.

Note

The surgeon should be prepared for vein grafting because the iliac flap vascular pedicle is rather short and vein grafts are necessary in up to 50% of cases.
6.8.7 Total Maxillectomy with Orbital Exenteration

When tumor resection extends from dorsal tongue to supraorbital rim, reconstructive options depend on the amount of remaining dentition. If adequate teeth and alveolar arch remain, prosthesis may be utilized. The use of a prosthesis that spans the defect from the oral cavity to the orbit is subject to cheek retraction over time and poor fit as well as the distracting appearance of an unblinking, expressionless eye. A superior approach is to complete the palate and alveolar arch with a prosthetic device in conjunction with a bulky myocutaneous flap, such as the abdominis rectus to fill the midface volume, including the orbit, as described by Cordeiro's group. This complex reconstruction resulted in a fair cosmetic result in 46% of patients, but normal or near-normal speech in 77%, and a soft diet in 54%. In order to achieve adequate bone volume for both the infraorbital and zygomatic region as well as the alveolar arch, any of the bony options described above can be utilized, but adequate soft tissue must be harvested to obliterate and/or line the orbital component of the defect. In those cases where there is intracranial communication, the skull base must be sealed as well.

Chepeha et al outlined their approach to orbital restoration in a series of 19 patients with orbital defects. The group with defects involving orbital exenteration and less than 30% of the bony orbital rim were reconstructed with the osteocutaneous forearm flap. In contrast, patients with orbital exenteration cavities only were reconstructed with fasciocutaneous forearm flaps. Finally, for radical orbital exenteration cavities with resection of overlying skin and bony malar eminence, these authors used osteocutaneous scapula flaps. Among 16 patients with greater than 4 months of follow-up, 10 were judged to have minimal or no facial contour deformity, 8 frequently engaged in social activities outside the home, and 5 of 9 patients who were employed preoperatively had returned to work. This group cited advantages of autologous tissue reconstruction of the orbit to include durability, minimization of defect size, avoidance of potential accidental displacement of a patch or prosthesis, and the tendency for other’s attention to be drawn toward the opposite, functional eye instead of a static ocular prosthesis. Additionally, when the eyelids and orbicularis oculi muscles remain unresected, the lids may be sewn together and skin color match and facial expression including the blink reflex is preserved.

6.9 Conclusion

Basic functional and aesthetic goals of maxillary reconstruction can now be achieved with good reliability and predictability. Further, combinations of microvascular free tissue transfer, local flaps, and/or maxillofacial prostheses may achieve a more ideal result than a single technique alone. Critical assessment of patients who were reconstructed compared to those who were restored with a prosthesis alone has demonstrated the value of this surgical undertaking. Limitations of present techniques that must be addressed include the need for restoration of the sinus cavities, the replacement of mucosa with mucosa instead of skin, and a more accurate replication of the complexities of the midfacial bones, their soft tissue coverings, and attached dentition. Osseointegration can plan an integral part in many of these defects for maximum retention for many types of maxillofacial prosthesis, especially for circumstances of constant functional demand. It is clear that no single flap or technique is sufficient to reconstruct midface defects in all cases. The choices should be tailored to the bony and soft tissue needs of each specific defect, denture-bearing potential of the native tissues, and available prosthetic support. Midface reconstruction will continue to require careful planning and a
multidisciplinary approach between the extirpative surgeon, reconstructive surgeon, prosthodontist, and radiation therapist to achieve long-term functional and aesthetic success. In all cases, the complexity of the techniques should always be matched to the desired goals of the patient as well as the needs of the defect.

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Management of Carcinoma of the Lateral Pharynx and Soft Palate

7 Management of Carcinoma of the Lateral Pharynx and Soft Palate

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7.1 The Lateral Pharynx

7.1.1 Introduction

Rise in incidence of lateral pharyngeal cancer has become an important public health issue in recent years. The increase in cases of oropharyngeal carcinoma associated with human papillomavirus (HPV) has stressed the importance of understanding this disease process and developing treatment techniques with improved outcomes and decreased morbidities. In this chapter, the epidemiologic history of the disease, recommendations for patient care, and the current status and future projection of this evolving field are discussed.

7.1.2 Etiology and Risk Factors

More than 90 to 95% of tumors of the oropharynx are squamous cell carcinoma (SCC) with the remainder being minor salivary gland tumors, malignant melanomas, sarcomas, lymphomas, plasmacytomas, and other rare tumors.1 The etiologies of lateral pharyngeal SCC can be categorized into two large subsets. The first is HPV-related disease and the second is HPV-unrelated disease. In the era prior to HPV-related disease, the development of lateral pharyngeal cancer, and specifically tonsil cancer, was correlated most strongly with smoking and alcohol consumption. These remain independent, dose-dependent, and synergistic risk factors, similar to other upper aerodigestive tract cancers.2 More than 90% of HPV-related carcinomas.14

Oral HPV infection is the most significant risk factor for the development of HPV-related oropharyngeal cancer. Infection with a high-risk HPV subtype (HPV16) has a greater than 14-fold increased risk of oropharyngeal cancer.15 Risk factors for oral HPV infection include increasing age, male gender, higher number of lifetime sexual partners, and increasing number of cigarettes smoked per day.16,17,18

Although the physician plays an important role in educating patients about a diagnosis of HPV-related disease, studies show that conversations involving the discussion of sexual risk factors are difficult for both the physician and the patient.19,20 As a physician, normalizing the diagnosis and emphasizing the positive prognosis are key points in educating patients and preventing feelings of blame or guilt.21 Common patient questions include those about the mechanisms of acquiring and transmitting HPV-related cancer.22 Patients should be informed that HPV is considered a sexually transmitted disease, but this can include acts such as kissing and that the infection may have been acquired many years or even decades prior to diagnosis. Patients with HPV-related oropharyngeal carcinoma should also be counseled that although HPV is transmitted through sexual activity, partners do not have increased oral HPV infection rates when compared to the general population.23

Note

When confronting a newly diagnosed patient with HPV-related disease, it is important to emphasize the positive prognosis as a key point to prevent feelings of blame or guilt that often afflicts patients.

7.1.3 Epidemiology

Traditionally, lateral pharyngeal cancer was most commonly diagnosed in the seventh or eighth decade of life; more recently, however, HPV-related disease has shifted epidemiologic trends. The incidence of oropharyngeal cancer, and specifically tonsillar SCC, has been rapidly increasing in many parts of the developed world due to the subset of oropharyngeal cancers...
caused by HPV infection. The United States is considered the epicenter of this epidemic where the incidence of HPV-related oropharyngeal cancer has increased by more than 200% since the late 1980s. Conversely, the incidence of HPV-unrelated oropharyngeal cancer has declined by 50% in the same time period. It is currently estimated that HPV infection is responsible for more than 75% of all oropharyngeal cancers diagnosed within the United States.

Note
It is currently estimated that HPV infection is responsible for more than 75% of all oropharyngeal cancers diagnosed within the United States.

The burden of this epidemic has primarily fallen on men younger than 60 years; incidence rates for adult men compared to the women in the United States are 7.3 and 2.2 per 100,000 people, respectively. A large nationally representative study of oral HPV infection among the United States’ population (aged 14–69) found that men had a significantly higher prevalence of any oral HPV infection compared to women (~10 versus ~4%, respectively); 1.6% of men had a high-risk oral HPV16 infection compared to just 0.3% of women in the United States. Oral HPV prevalence followed a bimodal distribution in regard to age; the first peak in prevalence was observed among those aged 30 to 34 years, followed by a second higher peak among those aged 60 to 64 years.

It is projected that the incidence of HPV-related oropharyngeal cancer is likely to continue increasing over the coming decade. Although highly effective prophylactic HPV vaccines have been available to the public since the mid-2000s, HPV vaccination is not expected to slow this rapid rise in HPV-related oropharyngeal cancer until at least 2060, when the first birth cohort to receive HPV vaccination reaches middle age. Likewise, because of low vaccination rates within the United States, HPV-related oropharyngeal cancer is likely to continue being a significant problem in the future despite the availability of highly effective vaccines.

Note
Oral HPV prevalence follows a bimodal age distribution. The first peak in prevalence is observed among those aged 30 to 34 years, followed by a second higher peak among those aged 60 to 64 years.

7.2 Anatomy of the Lateral Pharynx

The lateral pharynx largely includes the palatine tonsillar regions, which are located in the posterior lateral regions of the oropharynx. The tonsils are ovoid lymphoid structures encapsulated within a fibrous sheath within the tonsillar fossae. The tonsillar fossae are bounded by the palatoglossus muscle anteriorly and the palatopharyngeus muscles posteriorly. Superiorly, the tonsillar fossae join the soft palate. The inferior portions of the fossae form the glossoopalatine sulci. The lateral pharynx is closely related to the retromolar trigone, base of tongue, and the superior constrictor. Lateral and deep to the constrictor muscles lies the buccopharyngeal fascia; this fascial plane serves as an important barrier to spreading of cancer.

The blood supply to the region is provided by tonsillar branches of four arteries: ascending pharyngeal artery, ascending palatine artery, dorsal lingual artery, and the descending palatine artery. The peritonsillar plexus carries the tonsillar venous drainage to the lingual and pharyngeal veins and ultimately to the internal jugular vein. Tonsillar branches of the glossopharyngeal and lesser palatine nerves provide innervation to the palatine tonsils and lateral pharynx. The tonsils are composed of lymphatic tissue with crypts lined by specialized reticulated epithelium. It is thought that the specific cryptic structure of the tonsils is involved with the propensity for HPV to cause malignant transformation of tonsillar cells, however, the exact mechanism is unknown.

7.2.1 Pathology

More than 90 to 95% of tumors of the oropharynx are SCC with the remainder being minor salivary gland tumors, malignant melanomas, sarcomas, lymphomas, plasmacytomas, and other rare tumors. Given the rapidly growing HPV-related population, we will focus this discussion on the pathologic evaluation of these tumors. Considering that HPV-related oropharyngeal cancer is etiologically, clinically, and prognostically distinct from HPV-unrelated oropharyngeal cancer, routine HPV testing for all resected oropharyngeal SCCs is recommended. Importantly, the tissue evaluation must have the ability to discriminate a transient (not biologically relevant) HPV infection from a biologically relevant HPV infection that drives the carcinogenic process.

Expression of HPV oncoproteins E6 and E7 within a tumor is currently considered the best evidence for a transcriptionally
active (clinically relevant) HPV infection that is likely to be the driving force behind tumor development. Thus, in the research laboratory setting, detection of high-risk HPV E6/E7 messenger RNA (mRNA) expression is considered the gold standard method and is also the method by which the sensitivity and specificity of all other HPV assays are measured. However, this method is technically difficult to perform and thus its use has been mainly restricted for research purposes only.

Note
Expression of HPV oncoproteins E6 and E7 within a tumor is currently considered the best evidence for a transcriptionally active HPV infection. Detection of high-risk HPV E6/E7 mRNA expression is considered the gold standard method for linking HPV to carcinoma.

In clinical practice, commonly used methods of determining HPV tumor status include HPV DNA detection, p16 immunohistochemistry (p16 IHC), and HPV in situ hybridization (HPV ISH) (Table 7.1). Detection of HPV DNA by polymerase chain reaction (PCR) methods is a highly sensitive (100%) method for detection of HPV-related tumors. However, because of its ability to detect even trace amounts of HPV DNA, this method is also very susceptible to viral contamination and thus lacks adequate specificity (90%). p16 IHC has become a popular method given that it is a surrogate marker of an active HPV infection and allows for direct visualization of the marker within the context of the tumor specimen; p16 is an endogenous tumor suppressor protein that becomes overexpressed as a result of high-risk HPV E7 oncoprotein expression. While as a stand-alone test, p16 IHC has high sensitivity (97%), the specificity is inadequate (72%). HPV ISH is another commonly used method in tumor tissue sections. HPV ISH uses labelled DNA probes to hybridize to HPV type-specific DNA sequences allowing for direct visualization of HPV DNA within tumor cells. In contrast to p16 IHC, HPV ISH has a low sensitivity (93%), but high specificity (92%). Taking advantage of the high sensitivity of p16 IHC and high specificity of HPV ISH, combined p16 IHC and HPV ISH testing is the preferred clinical method for determining HPV tumor status. Compared to the research gold standard method, combined p16 IHC and HPV ISH testing has a sensitivity of 91% and specificity of 94% (Fig. 7.2).

Table 7.1 Testing methods for HPV-related carcinoma

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>100%</td>
<td>90%</td>
<td>Viral contamination</td>
</tr>
<tr>
<td>IHC p16</td>
<td>97%</td>
<td>72%</td>
<td>Low specificity</td>
</tr>
<tr>
<td>IHC HPV</td>
<td>93%</td>
<td>92%</td>
<td>Marginal sensitivity</td>
</tr>
</tbody>
</table>

Abbreviations: HPV, human papillomavirus; IHC, immunohistochemistry; PCR, polymerase chain reaction.

Note
The combination of the highly sensitive p16 IHC and high specificity of HPV ISH is the preferred clinical method for determining HPV tumor status demonstrating a sensitivity of 91% and specificity of 94%.

7.2.2 Clinical Presentation of Lateral Pharyngeal Cancer

SCC of the lateral pharynx most commonly presents as an ulcerated mass, fullness, or irregular erythematous mucosal changes in the tonsillar region (Fig. 7.3). Although HPV-related and HPV-unrelated SCC develop in similar anatomical regions, initial presentations vary. Since regional metastases can occur even with very small primary tumors, patients with HPV-related disease most frequently present with a neck mass as an initial symptom (51%). Patients with HPV-unrelated disease are more likely to initially complain of symptoms at the primary site: sore throat (53%), dysphagia (41%), or odynophagia (24%). Other less common presenting symptoms include globus sensation and poorly fitting dentures due to mass effect on the posterior gingiva. About 81 to 85% of patients will present in advanced stage disease (stage III or IV) due to the tumor’s ability to grow given the surrounding anatomy and its propensity for metastasis. Diagnosis may be delayed in cases of asymptomatic neck mass...
with an “unknown primary,” which requires an extensive diagnostic workup including imaging, examination under anesthesia in the operating room, and multiple directed biopsies or even resection of the entire tonsil or base of tongue to establish a diagnosis.50,51

Note
Unlike patients with tobacco- and alcohol-related oropharyngeal carcinoma who commonly present with odynophagia, patients with HPV-related disease most frequently present with a neck mass as an initial symptom.

Physical examination begins with a visual examination of oral cavity, tonsillar fossae, and retromolar trigone for masses or mucosal changes. Palpation of the tonsil may reveal immobility, which may indicate penetration through the constrictor muscle and therefore disease that cannot be effectively cleared to negative surgical margins. Trismus indicates deep invasion into the pterygoid muscles. Palpation of the base of tongue can help evaluate inferior spread. Visualization and palpation of the posterolateral pharynx may reveal a retropharyngeal carotid artery, which is important for operative planning as it is considered a contraindication for radical tonsillectomy. A nasopharyngoscope may be used to evaluate more distant spread to the vallecula, epiglottis, and hypopharynx. A complete neck examination should be conducted to evaluate for cervical metastasis.

Note
Because patients with HPV-related disease often present with regional metastasis and not uncommonly a very small primary tumor, they may require a thorough evaluation to identify the primary carcinoma.

Patterns of Spread of Lateral Pharyngeal Cancer

Locoregional
The surrounding anatomy of the tonsillar fossae allows for several potential directions of spread in more aggressive disease. Tumor spread to adjacent structures may include the soft palate, retromolar trigone, base of tongue, and posterior pharyngeal wall. Lateral spread in late-stage disease encroaches on the pterygoids, parapharyngeal space, and skull base, which may cause functional and neurologic symptoms.

Nodal Disease
Since most patients present with advanced-stage disease, nodal metastasis is common at presentation. Metastasis to ipsilateral levels II to IV may occur, with IIA being most common52 (> Fig. 7.4). Metastasis including levels I and V are associated with positive multilevel ipsilateral or contralateral nodes. Contralateral cervical metastasis is associated with T3–T4 stages, primary lesions close to the midline, and ipsilateral multilevel nodal involvement; in a study conducted prior to routine HPV testing of tonsillar cancer, rates of occult contralateral metastasis in excess of 20% were observed in patients with these tumor features and clinically positive, multilevel ipsilateral nodes. It is
also important to evaluate for retropharyngeal nodal metastasis, which is correlated with posterior pharyngeal wall invasion of the primary tumor, N stage III or IV, and contralateral nodal metastasis.

### 7.2.3 Diagnosis and Workup for Lateral Pharyngeal Cancer

After a complete head and neck examination with nasopharyngoscopy, evaluation should include imaging with contrasted CT scan or MRI of the head and neck. Review of the imaging should pay specific attention to extension of primary tumor and distance from midline structures, invasion of parapharyngeal fascia deep to the constrictor muscles, nodal metastasis including retropharyngeal nodes, and presence of retropharyngeal carotid artery. The National Comprehensive Cancer Network (NCCN) guidelines recommend chest imaging (CT or roentgenogram) in all patients with a diagnosis of oropharyngeal cancer. A positron emission tomography (PET)/CT is reasonable if there is concern for widespread metastasis or concurrent cancers (▶ Fig. 7.5).

For patients presenting with neck mass and unknown primary, or in whom neck metastases are questionable, a fine-needle aspiration (FNA) biopsy can be used to establish diagnosis. Core biopsies should be avoided, and excisional biopsies should be reserved for cases of significant diagnostic uncertainty. If an excisional biopsy is performed, the immediate surrounding lymphatic tissue should also be included to ensure complete removal of the mass and obviate revision surgery in that area, if a neck dissection is later indicated. Tissue from FNA biopsy can be sufficient for HPV testing and some of the specimen should be sent for this purpose if HPV status is unknown.54

**Note**

For patients presenting with neck mass and unknown primary, or in whom neck metastases are questionable, an FNA biopsy can be used to establish diagnosis. Core biopsies should be avoided, and excisional biopsies should be reserved for cases of significant diagnostic uncertainty.

HPV testing should also be conducted on the primary lesion. Although some large or exophytic tumors may be amenable to in-office biopsy, biopsies are frequently completed in the operating room in conjunction with extensive palpation for staging. A formal panendoscopy (laryngoscopy, bronchoscopy, and esophagoscopy) to evaluate for synchronous primary lesions of the aerodigestive tract may be considered for patients with a history of alcohol or tobacco abuse or who have additional symptoms. Because patients with oropharyngeal cancer may have functional impairment before or after surgical and/or nonsurgical therapy, nutrition and speech/swallow evaluation are important to consider prior to treatment, and at intervals during or after treatment, based on symptoms or signs of dysphagia, aspiration, and malnutrition. A complete dental evaluation should be performed before radiation therapy is undertaken. In patients with comorbidities in whom surgery is being considered, preanesthesia studies are recommended.

### 7.2.4 Prognostic Factors for Lateral Pharyngeal Cancer

HPV positivity is the single most important prognostic factor for survival among oropharyngeal cancer patients. Individuals with HPV-related tumors have a greatly increased chance of survival: 3-year overall survival is 80% among HPV-related patients compared to 57% for HPV-unrelated patients.55 Despite the better prognosis, approximately 10 to 25% of HPV-related oropharyngeal cancer patients will experience progression of disease within 3 years of treatment completion. Recently, HPV positivity has also been shown to be an important prognostic factor for progressive disease: 2-year overall survival for HPV-related oropharyngeal cancer patients following disease progression is 55% compared to 28% among HPV-unrelated patients.56

Conversely, advanced nodal disease is a predictor of poor prognosis. A prospective study of 156 patients with HPV-related oropharyngeal carcinoma treated with chemoradiation showed a 3-year disease-specific survival rates of 100%, 59%, and 74% for N1, N2, and N3 nodal disease, respectively.57 In patients with retropharyngeal node metastasis prior to treatment, rates of cervical node recurrence and distant metastasis are significantly higher, while overall survival and disease-specific survival are lower.58,59 A retrospective study of 208 patients with oropharyngeal SCC showed that regional recurrences were more common in patients with retropharyngeal adenopathy (45 vs. 10% without retropharyngeal node involvement) at 5 years.60 Evidence for the prognostic importance of extra-nodal extension (ENE) has been reported in the literature for decades.
Recent studies have shown, however, that the status of ENE is specific to HPV-unrelated cancers, and that positive ENE in HPV-related cancers does not significantly impact survival.\textsuperscript{115,116,117,118,119} The new American Joint Committee on Cancer (AJCC) staging system has taken these pathologic findings into consideration in prognostic evaluation for oropharyngeal cancers.

\section*{Staging}
Prognostic staging for lateral pharyngeal tumors fall under the larger category of oropharyngeal cancers. Historically, the AJCC has used the TNM staging system, based on anatomical risk factors, for oropharyngeal cancer staging.\textsuperscript{61} Traditionally, most oropharyngeal cancers were related to tobacco and alcohol use, which made uniform anatomical staging more reliable. HPV-related patients, however, have better survival outcomes when compared to HPV-unrelated patients in the same AJCC stage. Horne et al compared HPV-unrelated and HPV-related 4-year survival based on AJCC staging; HPV-unrelated cases survival rates were 61.8, 56.3, 61.1, and 55.8% for stages I, II, III, and IV, respectively, while HPV-related survival rates were 90.1, 96.1, 87, and 80.1% for stages I, II, III, and IV, respectively.\textsuperscript{62} Ang et al defined three overall groups by risk of overall death: HPV-related nonsmokers (low risk), HPV-related smokers (intermediate risk), and HPV-unrelated (high risk, except T2–T3 nonsmokers who were intermediate).\textsuperscript{63} It was found that although HPV-related disease has a favorable prognosis, adding tobacco use worsened overall survival.\textsuperscript{64,65} Additionally, recent studies have revealed the importance of ENE in cervical disease when considering the staging of lymph node metastasis. The latest 8th edition of the AJCC oropharyngeal staging system reflects these considerations, and has created two separate staging systems, one for HPV-unrelated disease, and one for HPV-related disease (\textsuperscript{66} Table 7.2, \textsuperscript{67} Table 7.3, \textsuperscript{68} Table 7.4, \textsuperscript{69} Table 7.5, \textsuperscript{70} Table 7.6, \textsuperscript{71} Table 7.7).

Several studies have proposed alternative staging systems based on additional risk factors that impact prognosis: HPV-related status, greater age at treatment, nononsillar primary site, comorbidities, and financial status to affect survival.\textsuperscript{66,67} Recently, O’Sullivan et al created a more prognostically accurate staging system for HPV-related oropharyngeal cancer by rearranging the TNM staging groups without the incorporation of nonanatomical risk factors.\textsuperscript{66} Importantly, this staging system redefined nodal categories to account for the significant decrease in 5-year overall survival found in N3 disease (59%) when compared to N0 to N2 disease (over 80%). The AJCC has developed a new staging system for HPV-related oropharyngeal carcinomas in the 8th edition of the cancer staging manual.

\subsection*{7.2.5 Treatment}

\textbf{Unimodal Therapy for T1–T2, N0–N1 Lateral Pharyngeal and Soft Palate Carcinoma}
Early-stage oropharyngeal cancer, including T0–T1, N0–N1 tumors, can potentially be treated with a single mode of therapy. According to NCCN guidelines, surgical resection or radiation therapy (RT) can be used safely.\textsuperscript{69} In the case of T2, N1 tumors, RT with chemotherapy is currently recommended; however, the effectiveness of surgery alone, specifically with minimally invasive surgery, is being investigated.\textsuperscript{70,71,72,73} For patients who are treated with surgical resection, adverse
pathologic features guide adjuvant therapy: postoperative radiation for perineural or lymphovascular invasion and/or N2 or greater neck disease and postoperative chemoradiation for positive margins and/or nodal extracapsular spread. For those patients who are treated with radiation, residual disease on posttreatment imaging or examination necessitates salvage resection.

In the case of surgical resection (see next section for surgical approaches), clinical examination and imaging guide management of the neck. A clinically positive neck requires dissection, which includes ipsilateral levels II to IV. Retropharyngeal nodes should also be evaluated clinically and dissected if found to be positive.

In patients with a clinically negative neck, elective neck dissection (END) of levels II to IV is generally considered a standard of care but remains a controversial issue. One retrospective study did not show statistically significant differences in overall survival, disease-free survival, or disease-specific survival in patients with END. Two retrospective studies showed improved regional control in patients with END versus observation, but similar disease-specific survival. Cases have been made for a randomized control trial to study the benefit of END in a clinically negative neck, which remains debated.

### Multimodal Therapy for T3–T4, N0–N3 Lateral Pharyngeal and Soft Palate Carcinoma

For more advanced disease, NCCN guidelines recommend multimodal therapy including chemoradiation, surgical resection followed by RT, or induction chemotherapy followed by RT. Surgical resection may require more invasive approaches, and management of the neck may involve more extensive dissection. Bilateral neck dissection is mandatory in bilateral clinically positive necks and for primary lesions close to or crossing the midline. Because of a high rate of occult contralateral disease, bilateral neck dissection should be considered in patients with multiple positive ipsilateral nodes and/or large (T3–T4) primary tumors. Elective retropharyngeal node dissection is uncommon, but may be considered for patients with posterior pharyngeal wall invasion, advanced nodal stage, contralateral node metastasis, and ipsilateral multilevel node involvement.

### De-Escalation for HPV-Related Disease

Studies have suggested that HPV-related SCCs have higher cure rates, decreased recurrence rates, and increased overall survival when compared to HPV-unrelated SCCs, regardless of treatment modality. As a result, some have suggested de-escalation of treatment for patients with HPV-related disease to reduce complications and morbidity associated with treatment, while maintaining similar oncologic results. Patient selection is critical in this process, and accurate testing for HPV-related status is required. Treatment de-intensification can be accomplished through decreased radiation doses, minimally invasive surgical approaches (transoral, see below), and the use of less potent chemotherapeutic agents. These proposed treatment protocols are being tested in several ongoing trials. De-escalation in HPV-related disease plays an important role in minimizing short- and long-term morbidity that results from treatment; however, patient selection plays an important role in the efficacy of treatment and oncologic results.

#### 7.2.6 Surgical Technique

The oropharyngeal anatomy allows for several approaches for tumor resection, however, there are some principles of operating in this region that endure, regardless of the procedure: (1) complete resection with appropriate margins, (2) maintaining a seal between the neck and pharynx, either through transoral approach or reconstruction, (3) protection and coverage of the carotid artery, and (4) hemostasis in an area that is highly vascularized (= Table 7.6).

Adequate margins are generally considered to be at least 5 mm or greater, but this is only a general guideline and margin assessment must take into account the grade and behavior of the tumor (“pushing” vs. “infiltrative”) and the anatomical site of the margin. Whereas margins in excess of 5 mm are easily obtainable in the soft palate and tongue for early tonsil cancers, the constrictor muscles and buccopharyngeal fascia that make up the deep margin are anatomically thin (2–3 mm). With careful anatomical orientation and margin assessment, it is possible to consider narrow margins that do
Management of Carcinoma of the Lateral Pharynx and Soft Palate

Table 7.6 The goals of surgical management of carcinoma of the lateral pharynx and soft palate

<table>
<thead>
<tr>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resection with negative margins</td>
</tr>
<tr>
<td>Maintain a seal between the neck and the pharynx</td>
</tr>
<tr>
<td>Protection and coverage of the carotid artery</td>
</tr>
<tr>
<td>Hemostasis</td>
</tr>
</tbody>
</table>

Note

Adequate margins are generally considered to be at least 5 mm or greater, but this is only a general guide. Margins in excess of 5 mm are obtainable in the soft palate, however, for tonsil cancers, the constrictor muscles and buccopharyngeal fascia that make up the deep margin are anatomically thin, providing a maximal deep margin of only 2 to 3 mm.

Transoral Approaches to the Lateral Pharynx

Several transoral approaches have been developed to address the resection of lateral pharyngeal masses including electrocautery, laser, and transoral robotic surgery. Overall, a movement toward minimally invasive surgical resection has been gaining support. Given their unique benefit-risk profiles, each approach plays a specific role in oropharyngeal tumor resection.

Transoral Lateral Oropharyngectomy

Huet first documented the transoral technique for resection of an invasive SCC of the tonsil in 1951. Since then, the technique has been adapted for use in several oropharyngeal cancer resections using electrocautery. Surgical technique as described by Holsinger is as follows. The ipsilateral ridge between the buccinator and superior constrictor muscles is initially identified through palpation. Next, the ridge is incised and extended inferiorly to the posterior floor of mouth and superiorly to the maxillary dentition. The tonsil is grasped and retracted medially, which identifies the plane deep to the superior constrictor that serves as the surgical margin. Dissection posteriorly to the prevertebral fascia allows for identification of the internal carotid artery. Some surgeons prefer to complete a neck dissection prior to transoral resection, which allows for location and protection of the carotid artery. Continuous medial retraction of the tonsillar specimen is important during this procedure as it reveals dissection planes and separates them from the carotid artery.

From here, the procedure will vary depending on the extent and direction of spread of the primary tumor. Resection of the soft palate, hard palate, base of tongue, and posterior pharyngeal wall may be incorporated with this technique. In general, however, the anterior and posterior tonsillar pillars are first transected superiorly, then inferiorly. Next, the stylopharyngeus and styloglossus muscles are identified and transected. Finally, the inferior margin is connected to the posterior pharyngeal incision created previously. If the soft palate remains largely intact, the defect is left to heal by secondary intention and does not require reconstruction.

The most common surgical complication is velopharyngeal insufficiency (VPI) such as nasopharyngeal reflux and hypernasal speech. These can be treated with the use of an obturator or prevented through reconstruction with posterior pharyngeal flaps or free tissue at the time of the initial surgery. Bleeding is also a complication of this surgery, although rare. Care must be taken to avoid damage of nearby vessels including the carotid artery. Because this technique utilizes the parapharyngeal space as the dissection plane, tumor invasion of this space is a major contraindication; invasion can manifest as fixation to the lateral pharyngeal wall, trismus, or mandibular invasion.

Transoral Laser Microsurgery

Transoral laser microsurgery (TLM) aims to complete conservative oropharyngeal tumor resections with decreased morbidity. TLM is conducted under microscopic visualization of the oropharynx using a laryngoscope or retractor for exposure. The depth of invasion is first estimated with proximal transection of the tumor using the CO₂ laser. Then, in several blocks, the tumor is excised from the bed. Each margin is oriented and sent for frozen section, and positive margins are then reexcised until complete negative margins remain. The goal is to remove tumor more precisely, while preserving the surrounding anatomy and minimizing morbidity.

Major surgical complications are rare using this method, however, postoperative bleeding can be fatal. Wilkie et al found that ligating the external carotid artery during neck dissection (completed before transoral resection) greatly reduced the incidence of major postoperative bleeding.

Transoral Robotic Surgery

Like TLM, transoral robotic surgery (TORS) is an alternative method for minimally invasive tumor resection. In this method, the surgeon uses robotic arms that allow for visualization of areas previously inaccessible transorally. TORS has been increasingly adopted as a minimally invasive method for complete resection of oropharyngeal masses. Like TLM, a major complication of TORS is bleeding.

Transcervical Approach

A transcervical approach allows for access to retropharyngeal nodes and tumors that have extended inferiorly to the base of tongue. First, the appropriate cervical lymphadenectomy is performed. The neck dissection at this level should be mindful of the mandibular branch of the facial nerve superficially and the hypoglossal, spinal accessory, and vagus nerves deeply. As dissection is carried superiorly along the great vessels, the hypoglossal and vagus nerves must not be separated, as they share fibers and separation can result in permanent injury to both nerves. Access to the tumor site requires the development of a plane deep to the mandible, and a complementary
transoral approach is useful in developing this plane and “delivering” the oropharyngeal structures through the neck. This allows for better visualization and dissection of tumors that deeply invade the base of tongue, which would be difficult to access with a transoral approach alone (▶ Fig. 7.6). The delivery approach, however, is not suited for tumors that have significant lateral spread into the glossopharyngeal sulcus, as the transoral incisions that allow for exposure may violate the tumor margin. In the case of previously irradiated necks, the development of a plane between the carotid artery and pharynx using a transcervical approach can serve to protect the artery.

Mandibular Swing

The median mandibulotomy approach with paralingual extension (mandibular swing) was first popularized due to its improved exposure to oropharyngeal tumors.\(^}\) As technology and visualization through transoral and transcervical approaches improved, however, the mandibular swing approach fell out of favor due to associated morbidity. Nevertheless, this approach may be beneficial in specific situations that require greater access to the pharynx, particularly in patients with anatomical or posttreatment changes that limit transoral access (e.g., narrow mandible, trismus).

To start, the appropriate neck dissection should be completed prior to the swing. An ipsilateral incision is made from the mastoid to the mentum, and then superiorly to divide the lower lip at the midline. The lip can be divided using a zigzag technique which minimizes lip contracture and visually disrupts the incision line (▶ Fig. 7.7a, b). Some authors describe an incision that follows laterally around the chin in the mental crease, but this may result in denervation atrophy of the mentalis muscle. Next, the periosteum of the mandible is elevated, and the mandible is divided. Preplating and/or stair stepping the mandibular incision allows precise reapproximation at the end of the procedure. A mucosal floor of mouth incision extends from the anterior midline to laterally and posteriorly on the side of the tumor. The contralateral side is then retracted, including the tongue, which allows for access to the lateral pharyngeal lesion. After resection of the tumor, the floor of mouth is closed with suture and the mandible is approximated using bone plates.\(^}\)

This method, although providing excellent exposure to oropharyngeal tumors, comes with several morbidities. For dentulous patients, dividing the mandible puts teeth adjacent to the incision at risk; in this case, it is important to evaluate the dental structure for more amenable locations for mandibular division (a large gap between teeth or an edentulous region). Risks of malunion, malocclusion, exposure of the plate, and delayed healing are higher in mandibulotomy cases. Finally, the lip incision is at risk for poor cosmetic outcomes with scarring. One study addressed this issue with a modified mandibulotomy without lip splitting, which has a less wide exposure.\(^}\)

Indications for Tracheostomy

Depending on the location and extent of the resection, a surgical airway may be required both to allow better access to the tumor by avoiding a transoral endotracheal tube, and for postoperative airway protection. Airway compromise after tumor resection may result from postoperative edema or aspiration. In both of these cases, a tracheostomy is useful to secure the airway during the convalescent period.

7.2.7 Complications of Treatment

The risks of both postoperative hemorrhage and dysphagia are significantly dependent on the extent of the resection and the method used. Although life-threatening, carotid artery hemorrhage is rare, a tumor resection with margins that abut the artery increases the risk. In cases with carotid artery exposure and/or expected postoperative radiation, consideration should be given to flap coverage of the artery. Long-term dysphagia and requirement for feeding tube are largely related to the extent of base of tongue resection. Dysphagia lasting beyond the immediate postoperative period is rare after resection of T1–T2 lateral pharyngeal cancers. Patients should be evaluated by speech and swallow therapists for dysphagia and
rehabilitation. Treatment includes placement of nasogastric feeding tube or a gastrostomy tube for more long-term feeding. Dieticians can tailor tube feeds to optimize nutritional intake for postoperative healing.

VPI can result in cases of extensive palatal resection for bilateral radical tonsillectomy. Please refer to the Complications section under the Soft Palate heading of this chapter for details about VPI and reconstructive options.

7.2.8 Posttreatment Surveillance

Posttreatment surveillance operates to follow recovery and monitor for recurrence. During each visit, a full head and neck examination and nasopharyngeal endoscopy (if indicated) should be completed. NCCN guidelines recommend posttreatment baseline imaging of the primary tumor site and the neck (if treated) is recommended within 6 months of treatment for T3–T4 or N2–N3 disease. Because of the increased frequency of multimodal treatment, consideration should be given to evaluating for complications of chemotherapy and radiation with lab values for liver, kidney, and thyroid function. Again, chest imaging should be completed regularly if indicated by history. A sample of postoperative surveillance schedule based on the 2016 NCCN guidelines is depicted in Table 7.7.

<table>
<thead>
<tr>
<th>Year</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1–3 mo</td>
</tr>
<tr>
<td>2</td>
<td>2–4 mo</td>
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<tr>
<td>3</td>
<td>4–8 mo</td>
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<tr>
<td>4</td>
<td>4–8 mo</td>
</tr>
<tr>
<td>5</td>
<td>4–8 mo</td>
</tr>
<tr>
<td>&gt;5</td>
<td>12 mo</td>
</tr>
</tbody>
</table>

7.3 The Soft Palate

7.3.1 Introduction

In general, isolated tumors of the soft palate are uncommon, accounting for approximately 2% of head and neck malignancies, and 15% of oropharyngeal cancers. Of these, 80% are SCC with the remaining 20% comprised of minor salivary gland neoplasms, lymphomas, melanomas, and other nonsquamous tumors. Several aspects of soft palatal cancer management such as staging and treatment algorithms overlap with those of the lateral pharynx, as they are frequently studied together as the oropharynx; however, because the soft palate is critical in
speech and swallow function, treatment of these tumors must be cognizant of restructuring the palate and long-term quality-of-life effects of therapy. A multidisciplinary approach, including coordination with speech and swallow therapists, maxillofacial prosthodontists, and nutritionists, is especially important in the treatment of these cancers.

### 7.3.2 Etiology and Risk Factors

Tumors of the soft palate are correlated with tobacco and alcohol consumption in addition to HPV exposure, unlike cancer of the palatine tonsils, however, soft palatal SCC is more often HPV-unrelated.\(^{108}\) Reports of the percentage of HPV-related SCC of the soft palate range from 16 to 38%,\(^{109,110,111,112}\) but may be contaminated by HPV-related tonsillar cancer that presents in the deep soft palate. Other risk factors include poor oral hygiene and mechanical irritation (such as ill-fitting dentures).

### 7.3.3 Anatomy

The soft palate is a midline soft tissue structure that separates the oral cavity and oropharynx from the nasopharynx. It forms the roof of the oropharynx and the floor of the nasopharynx. Anteriorly, it is continuous with the hard palate, while laterally, it is continuous with the superior portion of the tonsillar pillars. The uvula is suspended from the posterior portion of the soft palate. The soft palate is comprised of five muscles: tensor veli palatini, palatoglossus, palatopharyngeus, levator veli palatini, and musculus uvulae. The blood supply to the region is provided by the lesser palatine arteries and the ascending palatine arteries. The pharyngeal plexus of the vagus nerve innervates the muscles of the soft palate with the exception of tensor veli palatini, which is innervated by the mandibular branch of the trigeminal nerve.

Importantly, the soft palate serves as the anterior border of the velopharynx, which serves as a sphincter that prevents regurgitation of food or liquids into the nasopharynx during swallowing. The remainder of the velopharynx is comprised of the lateral and posterior pharyngeal walls. The velopharynx also plays a role in speech and the production of certain sounds. The soft palate plays an important role in the proper functioning of the velopharynx, which is discussed in the Complications section.

**Note**

Importantly, the soft palate serves as the anterior border of the velopharynx, which serves as a sphincter that prevents regurgitation of food or liquids into the nasopharynx during swallowing.

### 7.3.4 Clinical Presentation of Carcinoma of the Soft Palate

SCC of the soft palate most commonly presents as an ulcerated mass, fullness, or irregular erythematous mucosal changes.\(^{112}\) Similar to lateral pharyngeal tumors, patients with HPV-related disease most frequently present with a neck mass as an initial symptom, whereas patients with HPV-unrelated disease present with local pain or mass effect at the primary site (\(\rightarrow\) Fig. 7.8). In cases of asymptomatic neck mass with unidentified primary tumor, the nasopharyngeal surface of the soft palate can be a hidden site that should be examined with mirror or endoscopy.

#### Patterns of Spread

**Locoregional**

Primary soft palatal tumors are most frequently found on the oropharyngeal surface rather than the nasopharyngeal surface. From there, the tumor can spread along soft tissue planes to the tonsillar pillars and the base of tongue. Additionally, cancer cells can reach the cranium through perineural tracking along the palatine nerve.

**Nodal Disease**

Cervical metastasis is found in 20 to 45% of patients at the time of initial presentation.\(^{113}\) Because the soft palate is a midline structure, bilateral cervical metastases are more common. Lymphatic drainage to bilateral neck levels II–III is most common, although retropharyngeal lymph node involvement is also seen (\(\rightarrow\) Fig. 7.9).

**Note**

Because the soft palate is a midline structure, bilateral cervical metastases are more common. Therefore, bilateral neck treatment is warranted.

### 7.3.5 Prognostic Factors

The prognosis of a soft palatal carcinoma is impacted by anatomical elements. Tumor thickness greater than 3 mm is
correlated with an increased risk of nodal disease, and therefore, poorer prognosis. Additionally, tumor extension to the tongue base, across the midline, or across the palatine arch indicates more extensive disease and poorer survival.

Staging

Soft palate lesions fall into the larger category of oropharyngeal cancer; please refer to the AJCC guidelines as outlined in ▶ Table 7.2, ▶ Table 7.3, ▶ Table 7.4, ▶ Table 7.5, Table 7.6, and Table 7.7.

7.3.6 Treatment of Carcinoma of the Soft Palate

NCCN guidelines include the soft palate within the oropharyngeal treatment algorithm (see treatment section for lateral pharyngeal cancers). The extent of the tumor and posttreatment swallowing function are major considerations when selecting between surgical or radiation therapy treatment. Because of inadequate reconstructive techniques in the past, radiation therapy had been the favored treatment modality. With recent advances in reconstruction and prosthetics, however, surgical resection of soft palatal tumors has become more common.

External beam radiation, brachytherapy, or a combination has been effectively used to treat soft palatal cancers. In an effort to reduce long-term morbidity, intensity modulation and localized radiation may play a role in the treatment of less advanced tumors. A major drawback of primary radiotherapy with or without chemotherapy is the palatal scarring that occurs with therapy. This can be functionally debilitating. The xerostomia and fragile mucosa make obturator retention problematic. Chemotherapeutic agents such as cisplatin and 5-fluorouracil are used in multimodal therapy for more advanced tumors and the addition of chemotherapy often results in enhanced toxicity and functional impairment. Posttreatment rehabilitation for speech and dysphagia plays an important role in patient recovery and long-term quality of life.

Note

A major drawback of primary radiotherapy for treatment of soft palate carcinoma is the palatal scarring that occurs with therapy. This can be functionally debilitating and difficult to manage with prosthesis.

7.3.7 Surgical Technique

Resection of a soft palatal lesion is most commonly approached transorally using electrocautery or CO2 laser. Since the soft palate is a curved structure, it is important to note that the resection should remain perpendicular to the surface. Small, superficial defects that have not significantly altered the soft tissue anatomy may be allowed to heal by secondary intent or closed primarily. A palatal prosthesis is an alternative. For more extensive defects, several reconstructive methods using local tissues or free flaps have been described in the literature and are detailed in Chapter 8.

7.3.8 Complications

Most significantly, alteration of the soft palate anatomy may cause VPI. A large resection of the soft palate leads to inadequate closure of the velopharyngeal sphincter, which may allow food or liquids to enter the nasopharynx during swallowing. Shortening the soft palate also changes the dynamic function of the velopharynx in speech, resulting in hypernasal speech and articulation errors. Nonsurgical treatment options include the use of an obturator or palatal lift prosthesis (▶ Fig. 7.10a, b). For patients with unilateral palatal dysfunction, primary closure of one side of the velopharynx, while maintaining a nasopharyngeal port on the contralateral side, can result in a reasonable nasal airway and maintain velopharyngeal competence (▶ Fig. 7.11a–c). Surgical treatment options for larger defects ultimately look to improve palatal closure through increasing the length of the palate or tightening the levator veli palatini sling. The pharyngeal flap was first described in 1875; today, a superiorly based pharyngeal flap is used to correct for defects of the soft palate that have presented lateral wall function. Alternatively, a sphincter palatoplasty serves to decrease the size of the velopharyngeal gap. Overall, reconstruction of a dynamic structure like the soft palate is challenging and serves as a major limitation to surgical resection of tumors.
7.4 Clinical Cases

7.4.1 Case 1: Tonsil Cancer with Retropharyngeal Node

Clinical Presentation
A 61-year-old man with a 35 pack-year history of tobacco use presents with worsening right throat pain in the last 3 months.

Physical Examination
The patient has a 3.5-cm ulcerative lesion of the right tonsil with extension into the tonsillar pillars (Fig. 7.3). On palpation, the tonsil is immobile and adheres to the lateral pharyngeal wall. Cervical lymphadenopathy of level II is noted on examination.

Diagnosis and Workup
PET/CT scans of the neck (Fig. 7.12) and chest were performed, which revealed a 3.7-cm left tonsillar mass with invasion of the constrictor muscle. Imaging also revealed ipsilateral lymphadenopathy: three level II and III nodes and one retropharyngeal node; each node was less than 25 mm. The chest CT did not show any concerning lung nodules. Patient was sent for preoperative anesthesia evaluation prior to biopsy and panendoscopy. Biopsy of the tonsil lesion showed moderately differentiated HPV-unrelated SCC, and the panendoscopy was negative for a second malignancy.

Options for Treatment
This patient presents with an HPV-unrelated T2N2b tonsil cancer. Examination and imaging suggest deeper invasion of the constrictor muscles, which is a contraindication to surgical resection. Moreover, the patient has multilevel ipsilateral cervical and retropharyngeal lymphadenopathy, which increases the risk of contralateral disease. In this case, treatment of the contralateral neck should be considered. This disease could be treated with concurrent chemotherapy and radiation therapy or with induction chemotherapy followed by radiation therapy.

Treatment: concurrent chemotherapy and radiation therapy to the right tonsil and bilateral neck and retropharyngeal lymph nodes. A high-dose cisplatin regimen was used concurrently with 70-Gy radiation therapy; intensity-modulated radiation therapy was used to minimize radiation to the parotid gland. The patient responded appropriately to treatment without residual disease on posttreatment PET/CT scan.

Summary
Extension of the tumor through the constrictor muscles is a relative contraindication to surgical resection. With this extensive disease, the patient would require postoperative chemoradiation after surgery, so a primary chemoradiation approach is usually preferred. Because multilevel nodal metastasis is associated with increased risk of contralateral neck disease, it is important to consider treatment of the contralateral neck.
7.4.2 Case 2: HPV and De-Escalation

Clinical Presentation
A 48-year-old nonsmoker presented to an outside ENT with right tonsil bleeding. A simple tonsillectomy was performed, which revealed a 0.4-mm focus of p16+ SCC, extending to within less than 1 mm of the deep-inked margin. No perineural or lymphovascular invasion was detected.

Physical Examination
The right tonsil bed shows healing eschar. The anterior and posterior tonsillar pillars are intact and without mucosal abnormalities, as is the base of tongue and palate. The neck reveals no adenopathy.

Diagnosis and Workup
Postoperative PET/CT scanning performed at the outside hospital revealed a 9-mm right level III lymph node with indeterminate uptake. An MRI was subsequently obtained demonstrating clean tissue planes deep to the tonsillar bed.

Options for Treatment
This patient has an HPV-related, T1 tonsil cancer, resected with negative but very close margins. Adequate resection would be considered 5 mm, or at least to the depth of the buccopharyngeal fascia. Radiographically, the patient has questionable N1 disease. In this patient, either a surgical or nonsurgical approach is feasible. As this patient has HPV-related disease, de-escalation might be considered in the setting of a defined clinical protocol for this purpose.

Treatment of the Primary Tumor
The primary tumor has not been adequately treated, due to the close margins. Therefore, he must either have a reexcision of the site via lateral oropharyngectomy, or chemoradiation. In this patient, we elected for a completion oropharyngectomy, which demonstrated no further tumor and provided an additional margin of constrictor muscle and buccopharyngeal fascia.
Management of Carcinoma of the Lateral Pharynx and Soft Palate

**Treatment of the Neck**

The neck can be treated with either surgery or chemoradiation, and treatment should be unilateral given that this is a small, lateralized tumor with no evidence of advanced neck disease or retropharyngeal nodes. Since this patient was having surgical treatment at the primary site, a unilateral elective neck dissection was performed revealing a single, level III lymph node with a 2-mm focus of p16+ SCC and no extracapsular spread. The final stage was T1N1. No adjuvant treatment was administered, and the patient began a surveillance program with interval scanning and examination.

**Summary**

Small, HPV-related tonsil cancers can be treated with surgical and nonsurgical approaches. Based on current evidence, the ipsilateral neck should be treated and the contralateral neck only reserved for larger tumors or for multilevel ipsilateral nodal disease. Adequate surgical margins are considered to be 5 mm, or at least surrounding unininvolved natural tissue planes such as the buccopharyngeal fascia. Adjuvant treatment after surgical approaches is reserved for close or positive margins, perineural invasion or lymphovascular invasion at the primary site, and N2 or greater neck disease and/or extracapsular spread.

7.4.3 Case 3: Bilateral Neck Dissection for Soft Palate Lesion

**Clinical Presentation**

A 62-year-old woman with a history of moderate alcohol use and smoking presents with a lesion on the left soft palate which was noticed by her dentist. She has no complaints and has never noticed the mass before. She denies dysphagia and odynophagia.

**Physical Examination**

One-centimeter ulcerated mass on the lateral aspect of oropharyngeal soft palate extending to the superior aspect of the anterior tonsillar pillar.

Palpation reveals an otherwise mobile soft palate.

**Diagnosis and Workup**

CT scan showed a 12-mm lesion of the left soft palate without extension into surrounding structures and an 11-mm right level III node. Panendoscopy did not reveal a second malignancy, and biopsy of the mass showed well-differentiated HPV-unrelated SCC.

**Options for Treatment**

This patient has a T1N1 HPV-unrelated SCC of the soft palate. Options include definitive RT, concurrent chemoradiotherapy (CRT), or surgical resection. Because the lesion involves the soft palate, a midline structure, bilateral neck treatment is included with these options.

**Treatment of the Primary Tumor**

The primary tumor was excised with 5-mm margins, margins were negative on final pathology, but lymphovascular invasion was detected. Primary reconstruction was performed with primary closure, leaving a right nasopharyngeal port.

**Treatment of the Neck**

Bilateral neck dissections of levels II to IV. Pathology confirmed three positive nodes in the right neck (levels II and III) without extracapsular spread. Final staging was T1N2b. This patient underwent postoperative radiation therapy given the advanced nodal disease.

**Summary**

Surgical resection of the soft palate is limited by reconstructive options, in small lesions with minimal deep invasion, local reconstruction offers sufficient tissue for palatal function. Midline structures, like the soft palate, require bilateral neck treatment. Adjuvant therapy is recommended for positive margins, advanced neck disease, and adverse pathologic features such perineural and lymphovascular invasion, and extracapsular spread.

7.5 Conclusion

1. Diagnosis of HPV-related oropharyngeal carcinoma impacts prognosis and treatment, the current AJCC staging system is less accurate for these cancers and will likely undergo revision.
2. Patient education about HPV-related disease is critical; there are several resources that discuss important facts with techniques to address difficult patient questions.
3. Balancing effective treatment against morbidity has become important in the era of HPV-related cancers, as they have improved overall prognosis and better treatment response. Clinical trials are currently ongoing to examine treatment de-escalation in oropharyngeal cancer.
4. Treatment of a primary soft palate lesion is dictated by long-term functionality, surgical resection of the soft palate is limited by the ability to reconstruct the defect.
5. Bilateral neck treatment should be considered for soft palate tumors and all tumors that approach midline. Consideration of contralateral neck treatment should be given in cases with advanced, multilevel ipsilateral neck disease and/or retropharyngeal nodes.

**References**


Management of Carcinoma of the Lateral Pharynx and Soft Palate


Management of Carcinoma of the Lateral Pharynx and Soft Palate


Reconstruction of the Lateral Pharynx and Soft Palate

8.1 Introduction

The oropharynx is among the most complex reconstructive challenges in the head and neck. It is vital to efficient swallowing and unparalleled in importance for prevention of nasal regurgitation and velopharyngeal insufficiency (VPI). Its structures are delicate, yet necessary and complementary in generation of the tongue propulsive force required to successfully send a bolus past the larynx and into the cervical esophagus. The soft palate allows for closure of the nasopharynx during speech and between swallowing and it is underappreciated until its loss causes chronic nasality issues for which reconstruction is difficult to replicate perfectly. Furthermore, the lateral pharynx provides important separation from the parapharyngeal space and coverage of the carotid sheath, while adding muscular constrictors useful in closure of the pharynx.

The last decade has seen resurgence in surgical approaches to the lateral pharynx and soft palate with transoral robotic surgery (TORS) and transoral laser surgery. This has led reconstructive surgeons to develop novel strategies to meet the reconstructive needs of patients undergoing these resections. Formerly, large open access via midline or lateral mandibulotomy allowed reconstruction to take place in an open field. Though challenges existed, the open approaches generally allowed reconstruction to take place from inside to out as the wound and mandibulotomy were sequentially sealed (Fig. 8.1, Fig. 8.2).

Newer transoral surgical approaches benefit patients by decreasing the sequelae of access incisions and major approaches, while limiting visualization for reconstruction. Similar to the ablative transoral story, the reconstructive surgeon has learned to respond to new and evolving challenges as the ablative field expands in that area. As such, the field of minimal access lateral pharynx and palate reconstruction has only recently evolved and produced recommendations and indications for various approaches. Indeed, it is recognized that some defects heal best through secondary intention, while others require local flap coverage (facial artery myomucosal [FAMM], buccal fat flap, palatal island flap), some are best served by regional flap coverage (submental island flap, supracleavicular flap, temporoparietal flap), while others are still best reconstructed with free tissue transfer (radial forearm flap, ulnar flap, anterolateral thigh flap).

8.2 Relevant Anatomy

8.2.1 General Anatomical Considerations

The lateral pharynx is a mucosa-lined structure with underlying constrictor musculature. The palatine tonsil lies within the

Successful reconstruction of the lateral pharynx and soft palate is complicated to define. Successful reconstruction of the pharynx begins with separating the oropharynx from neck contents and carotid. Yet, it is defined more intricately in quality of life (QOL), and freedom from VPI with good quality voice. Swallowing has been correlated with maximizing QOL; these structures strike a key balance in being important to survival, due to the anatomical proximity to the carotid, and important to function. The creation of defects is largely dependent on resections as outlined in the previous chapter. The focus of this chapter is to describe the strategies used to successfully rebuild the structure and function of the pharynx and soft palate.

Note

Transoral surgical approaches benefit patients by decreasing the sequelae of access incisions and major approaches, but they limit visualization for reconstruction.

Fig. 8.1 Midline mandibulotomy with resection of tumor. This is a conventional approach used to gain access to the posterior pharynx and base of tongue.
tonsillar fossa superficial to the superior constrictor. Deep to the tonsil lies the pharyngobasilar fascia followed by the muscle layer. Deep to the muscle lies the buccopharyngeal fascia layer, then the parapharyngeal space. A complete review of the anatomy of this space is beyond the scope and relevance of this chapter, however, the space contains the carotid sheath and its important contents. If a connection is created to this space during ablative surgery, the risk of fistula and carotid blowout is significantly increased without successful reconstruction.

The palate is a multilayered structure with mucosal lining on the nasopharyngeal side, muscular structure of the soft palate with neurovascular structures in the middle layer, and mucosal lining on the oropharyngeal side. The muscles are closely associated with the superior lateral pharynx and tonsillar pillars. The soft palate functionally allows for elevation of the palate and closure and creation of velar consonants in speech.

8.2.2 Muscular and Neurovascular Anatomy

The soft palate consists of five paired muscles: tensor veli palatini, palatoglossus, palatopharyngeus, levator veli palatini, and musculus uvulae.

The tensor veli palatini extends from the medial pterygoid plate and eustachian tube between the medial plate and muscle ending as a tendon that wraps around the hamulus before inserting into the palatine aponeurosis. It is innervated by the medial pterygoid nerve, a branch of the mandibular nerve (V3)—the remaining muscles are supplied by the pharyngeal plexus (from the vagal and glossopharyngeal nerves). When activated, the muscle acts on the soft palate to draw it superiorly and obstruct the palate against the posterior pharynx.6

Palatoglossus arises from the palatine aponeurosis and extends inferiorly to comprise the glossopalatine or anterior pillar of the tonsil fossa. This muscle is innervated by the pharyngeal plexus. Its major function is in the elevation of the posterior tongue and closure of the tongue against the lateral pharynx and palate.6

Palatopharyngeus is a muscle shaped similar to palatoglossus that creates the posterior pharyngeal pillar. It is divided into two portions by the levator veli palatini. The two segments join in the midline with the opposite muscle and inferiorly with the stylopharyngeus where both muscles insert into the posterior border of the thyroid cartilage. Innervated by the pharyngeal plexus, it acts to pull the pharynx upward over a bolus of food to prevent food entry into the nasopharynx.6

Levator veli palatini arises from the petrous temporal bone and medial eustachian tube. It splits the palatopharyngeus ending in interdigitating fibers at the midline palate. During swallowing, the pharyngeal plexus activates the muscle, and elevates the soft palate. It is the primary palatal elevating muscle of the palate.

Musculus uvula lies within the uvula acting to shorten or broaden it. This action can help close the nasopharynx during swallowing. It is innervated by pharyngeal plexus nerves. The uvula is used in some languages to create uvular consonants, produces thin saliva that aids in pharyngeal moisture, and is generally considered an accessory speech organ.

8.3 Evaluation of Pharynx and Palate Defects and Options for Reconstruction

Optimally, the planned resection will leave a known defect within a reasonable range. The use of preoperative scanning allows the team to reliably predict whether a through-and-through defect will be created and whether the carotid will be exposed due to retropharyngeal course.2 In addition, preoperative endoscopy and physical examination should anticipate the
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extent of soft palate removal. Rarely does the defect considerably extend well beyond the predicted deficit. Therefore, it is advisable to develop a reconstructive plan based on the expected resection with contingency plans available. It is recommended to prepare for local, regional, and free tissue options in most cases to prevent the need to prep or consent during the operation, especially where the extent of defect may be unclear.

The need and type of reconstruction that will best serve the patient is not solely based on the tumor (T) size, given the important functional and anatomical proximity considerations of this region. It is very possible to have a T1 tumor of the tonsil that may require a free flap if carotid exposure is expected, whereas a large T2 tumor may be exophytic and expose no deep structures or palate. Meanwhile, a small tumor of the palate will almost certainly require reconstruction to prevent VPI from tissue insufficiency or adynamic tissue. Genden and colleagues developed a reconstructive algorithm based on anatomical site involved and vascular pattern. They delineated that the amount of palate involved and major vessel anatomy, which are the two key considerations—most of which will be predictable preoperatively.

The only factor that cannot be completely predicted is whether a connection will be created to the neck. With larger and deeper tumors this is a greater risk, and it is also somewhat dependent on the timing of neck dissection. If a connection is created, there should be a clear indication for reconstruction as well.

Based on their algorithm and classification system, de Almeida et al evaluated the functional outcomes after surgery with MD Andersen dysphagia index (MDADI) and velopharyngeal insufficiency quality of life (VPQOL) surveys. The majority of defects were class II (49%) followed by class I, IV, and III (34, 14, and 3%, respectively). It was found that no significant difference in QOL score was noted between the four classifications. Clearly, the method of reconstruction employed weighed heavily in the results achieved. Free flaps were most likely to be utilized for classes III and IV defects (67 and 46% of those cases). A univariate and multivariate analysis of age, sex, class, tumor size (2 cm tipping point), defect size (8 cm tipping point), and adjuvant therapy is made; the results demonstrate that only external beam radiation therapy (XRT) predicted for lower MDADI score with a mean follow-up of at least 6 months.

### 8.4 Classification of Pharynx and Soft Palate Defects

Genden and colleagues divided TORS defects into four types (>Table 8.1). Types I and II were defined by absence of fistula, carotid exposure, and less than 50% of palate resected. Type I involved only one subsite whereas type II included more than one. Types III and IV had one of the three major defining characteristics positive with type IV including more than one subsite. Radiation exposure in the past was not included in this classification, but was considered important in decision making. Other authors and surgeons have considered the palatal involvement of 50% to be a high number to consider as tipping point for converting a local flap to regional or free tissue. Also lacking in this classification is the volume of tumor resected. For instance, a large resection of a bulky or deep tumor may leave a deficit of parapharyngeal bulk that would not be adequately replaced by a local pharyngeal flap. In some cases, it is advantageous to create bulk in reconstruction to divert the food bolus toward the sensorium, treatment naïve, side. At the author’s institution, one-third defect of the palate is considered large enough for regional flap, and in some cases free tissue. Therefore, adding tumor volume and XRT history, plus considering reconstruction for one-third defect of palate, are signs of the evolving reconstructive TORS field.

#### 8.4.1 Types I and II Defects

A type I defect does not connect to the neck, expose carotid, and comprises less than 50% of the palate and includes one subsite only—in the case of lateral pharynx and palate, it would encompass only the palate or the pharynx. Secondary considerations such as the patient anatomy with respect to tongue volume and palate position may also play an important role in selecting reconstructive options (>Fig. 8.3).

Type II defects mirror type I but include two subsites. The loss of both lateral pharynx and palate tissue creates a larger deficit in the functional unit that unites palate to lateral pharynx and allows closure of the nasopharynx and propulsion of food boluses (>Fig. 8.4).
8.4.2 Types III and IV Defects

Types III and IV defects include either a communication into the neck, carotid exposure, or greater than 50% of the palate involved (▶ Fig. 8.5). Additionally, type IV includes more than one subsite included in the resection (▶ Fig. 8.6).

8.5 Options for Reconstruction
8.5.1 Secondary Intention

It is important to any reconstructive algorithm to realize when no reconstruction is the best option (▶ Table 8.2). Experience with transoral tonsillectomy and the healing process afterward lends confidence to the strategy of allowing the pharynx to heal without flap surgery.

Patient Selection

In types I or II defect cases, even where the pharyngeal constrictor has been resected, the wound bed often heals adequately with sensate mucous membrane. The more lateral the defect, the more likely it is to achieve good function without reconstructing, and the author favors some reconstruction when the palate has one-third involvement after resection.

Note
The more lateral the defect, the more it will achieve good function without the need for reconstruction.
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Surgical Technique and Considerations
After resection the wound bed is tested to see if sign of fistula is present. If neck dissection is done simultaneously, the neck can be examined to determine if fistula is present. The tonsil bed should be carefully inspected for carotid exposure. If no fistula or carotid exposure is seen, the wound is dried and left to heal.

Perioperative Management
Patients can be observed for clinical evidence of fistula development and fed a soft diet once tolerable.

Pearls
- Secondary intention should be reserved for type I defects, primarily of the lateral pharynx.
- Resections that include two subites with significant loss in each large volume, carotid exposure, or fistula require reconstruction.

8.6 Locoregional Flaps in Velopharyngoplasty

8.6.1 Posterior Pharyngeal Flap or Palatal Island Flap

de Almeida et al reviewed their experience with reconstruction after TORS and demonstrated that the majority of patients requiring reconstruction are those with palate and tonsil defects. Thirty-nine percent of these were reconstructed using an advancement flap (posterior pharyngeal flap), or local advancement flap (25%). Local advancement can be from posterior pharyngeal wall, with or without a relaxing incision, or from palate, most formally as a palatal island flap. The cohort included patients with class I to IV defects and the class of defect was not significant in predicting poor swallowing outcome in the MDADI.14

Patient Selection
A posterior pharyngeal flap is known to be effective in treating patients with VPI from a variety of pathologies. Patients with types I and II defects involving the palate or upper pharynx are the optimal candidates. When the soft palate defect extends anteriorly to abut the hard palate, the posterior pharyngeal flap would be too long to maintain blood supply, and a palatal island flap is preferred. The author generally chooses between the two bases on how much anterior–posterior resection has occurred—when more than two-thirds of anterior palate is resected, the palatal island flap is used.

Table 8.2 Reconstructive options after lateral pharyngeal and palate resections

<table>
<thead>
<tr>
<th>Reconstruction</th>
<th>Defect types</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary intention</td>
<td>I, some II</td>
<td>Least invasive</td>
<td>Time to heal, risk of radiation ulcer</td>
</tr>
<tr>
<td>Posterior pharyngeal flap or palatal island flap</td>
<td>I, some II</td>
<td>Locally available, minimally invasive</td>
<td>Thin tissue, limited volume</td>
</tr>
<tr>
<td>FAMM flap</td>
<td>I, some II</td>
<td>Locally available, minimally invasive</td>
<td>Thin tissue, limited volume</td>
</tr>
<tr>
<td>Buccal fat flap</td>
<td>I, some II</td>
<td>Locally available, minimally invasive</td>
<td>Thin tissue, limited volume</td>
</tr>
<tr>
<td>TPF flap</td>
<td>I and II</td>
<td>Regional, larger volume</td>
<td>Additional incisions and risk to facial nerve</td>
</tr>
<tr>
<td>Submental island flap</td>
<td>I–IV</td>
<td>Large skin paddle regionally available</td>
<td>Venous congestion at distal flap</td>
</tr>
<tr>
<td>Regional muscle flaps</td>
<td>I and II</td>
<td>Support other closures with another layer</td>
<td>Typically not able to close entire defect</td>
</tr>
<tr>
<td>Radial and ulnar free flaps</td>
<td>I–IV</td>
<td>Pliable large skin paddle</td>
<td>Free tissue with associated risks of failure</td>
</tr>
<tr>
<td>Anterolateral thigh flap</td>
<td>I–IV</td>
<td>Skin, fascia, and muscle available</td>
<td>Thick flap, less pliable to inset</td>
</tr>
</tbody>
</table>

Abbreviations: FAMM, facial artery myomucosal; TPF, temporoparietal fascia.
Surgical Technique and Considerations

Posterior pharyngeal flaps may be superiorly or inferiorly based. Superiorly based flaps are preferred for soft palate reconstruction due to favorable vector of pull. Dissection through mucosa and posterior pharyngeal muscle is performed and the flap is rotated into the defect and secured with absorbable suture. The donor site is left to either heal by secondary intention, or preferably, closed primarily to further tighten the pharyngeal sphincter and recreate uninterrupted muscle ring. No attempt to remucosalize the muscular side is made, as it is quick to regrow in the viable flap. Dehiscence is possible particularly in the larger defect (greater than 33%) of the soft palate. The flap is robust in its ability to rebuild smaller defects, less than one-third of the soft palate, lateral and not far anterior. The radiated patient is at a higher risk for poor wound healing and dehiscence, thus care should be taken to not overextend the flap or place under tension (▶ Fig. 8.7).

Note

The radiated patient is at a higher risk for poor wound healing and dehiscence, thus care should be taken to not overextend the flap or place under tension.

The palatal island flap is a useful utility flap that can be rotated based on the greater palatine vessels. Most of the palate can be rotated pedicled on a unilateral side blood vessel, and used to reconstruct large surface areas of the superior tonsil and soft tissue palate. An incision is made posterior to the maxillary dentition from molar to molar, down through mucosa and periosseum. An elevator is used to lift the mucosa and periosseum off of underlying bone. The contralateral pedicle is preserved to the remaining mucosa and palate, while the ipsilateral pedicle is isolated and visualized. The periosseum surrounding these vessels can be released to improve rotation arc. The flap can then be transposed to the defect of the soft palate, or upper tonsil. The thick mucosa and periosseal layers provide multilayered tissues to suture into the defect.

Fig. 8.7 (a) Transoral Robotic Surgery (TORS) tonsil and palate defect repaired with a pharyngeal flap to partial close pharyngeal defect. (b) The pharyngeal flap is rotated over the defect and sutured to the nasal mucosa of remaining soft palate to decrease the nasopharyngeal aperture and prevent VPI.

Perioperative Management

The strength of the sutures holds together the closure in the first days and weeks after surgery. Therefore, the closure should be protected with modified diet (typically soft diet until postoperative office visit). The author generally advises patients to limit speech and activity in a fashion similar to that recommended after tonsillectomy. The goal of these modifications is to lessen stress on the suture line. Typically, discomfort limits patient activity naturally, yet it is worthwhile emphasizing these minimal limitations.

Pearls

- Type I defects are well suited for either posterior pharyngeal or palatal island flap reconstruction.
- Some type II defects with minimal multisite involvement may be adequately reconstructed with local tissue by performing pharyngoplasty or velopharyngoplasty.
- When local tissue is used, it is important to thoroughly elevate and rotate the tissue to allow for tension to be minimized.
- The goal of pharyngoplasty is to narrow the aperture to the nasopharynx, and to make use of the remaining preserved palate muscle to allow for close to normal function.

8.6.2 Facial Artery Myomucosal Flap

The FAMM flap is a myomucosal flap that includes the buccal mucosa, buccinator, and facial artery into an axial pattern rotation flap. It is best described in its use for small-to-moderate floor of mouth or lateral tongue defects, but has also been used for oroantral fistula, oropharynx defects, and lip defects among others. It has a generally reliable blood supply with typical issues of distal blood supply pending the length of flap needed.
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Patient Selection
FAMM flaps may be pedicled superiorly or inferiorly; if inferi-orly pedicled, the vessels enter the flap near the retromolar trigone and extend toward Stensen’s duct. Typically, when used for pharyngeal reconstruction or palate reconstruction, either flap allows for reach to the midline palate if necessary. The flap provides excellent length but is limited in width due the parotid duct location. Partial-thickness defects of the palate that are relatively thin in width are ideal for FAMM reconstruction. Previously radiated patients are at risk for poor venous outflow to the flap, which is typically supplied via a venous plexus rather than the facial vein. Patients in whom external scars avoidance is desirable, non-hirsute tissue is a priority, and same field surgery (as ablation) is useful, a FAMM flap should be considered. The ideal defect is small-to-medium in size and thin tissue such as floor of mouth or limited glossectomy or pharyngectomy.

Ayad et al. have catalogued the use of this flap in a systematic review indicating a thorough list of uses reported. In addition, Bonawitz and Duvvuri described the use of FAMM flaps for pharyngeal reconstruction with a robot-assisted harvest technique. In their limited series, the FAMM flap provided adequate rotation and tissue stock for soft palate defects up to 5 cm in size, sometimes employing bilateral flaps to rebuild near total soft palate defects. In addition, this flap is useful in secondary palate reconstruction after initial reconstruction results in VPI, or nasal regurgitation. It can provide additional reconstructive material that can augment previous reconstruction enough to improve these troublesome symptoms.

The use of the FAMM flap is not recommended in cases of diffuse dysplasia as the rotated flap could bring abnormal tissue to the area of reconstruction. Some studies suggest that prior XRT leads to higher rates of necrosis, but the series are relatively small and may be due to facial artery anomalies and radiation. Artery Doppler can help combat issues encountered after XRT if the flap is felt to be useful.

Surgical Technique and Considerations
The inferiorly based FAMM flap is drawn out extending from the third molar on the side of use, in a superior direction. The flap consists of mucosa, buccinator muscle, and facial artery with venous plexus. The inferiorly based flap is antegrade flow through the facial artery and can be elevated from distal to proximal. The flap is marked out with attention to designing at least 2 cm base in order to preserve venous drainage. The flap is marked out 1 cm posterior to oral commissure, and posteriorly bound by the location of Stensen’s duct. A Doppler can be used to trace the facial artery from the area at the second and third molar toward the gingivobulbar sulcus superiorly. The more distal the flap taken, the more random the blood supply will become resulting in an incidence of distal necrosis of approximately 10%. The facial artery can be identified surgically by incising distally and raising the flap from distal to proximal, or identifying it proximally and using direct visualization to further delineate the flap size. Most flaps are then rotated over the retromolar trigone toward the soft palate or lateral pharynx. Some authors choose to have patients wear a bite block for several days after the surgery to avoid biting the flap base. The flap can be divided at 3 weeks following the initial surgery. Modifications exist in the flap design with some advocating a single-stage flap. The donor site is usually closed primarily when less than 3 cm in width, but can be reconstructed with buccal fat if concern over contracture exists.

Superiorly based FAMM flaps follow similar steps to the inferiorly based version. The base of the flap is switched with gingivobulbar sulcus as the base. The size and reconstruction of donor site are the same for both flaps. Ayad et al. have indicated that sectioning of the pedicle is necessary 67% of the times it is used. Multiple modifications of the FAMM flap have arisen, but they are not of use in the reconstruction of the pharynx at this time.

Perioperative Management
Postoperative management of FAMM flaps is aimed at reducing the rate of complications. The reported rate of complications is 12.8% and consists largely of necrosis (partial 12.2%, complete 2.9%), venous congestion (5.6%), hematoma, dehiscence, and infection. As with any mucosal surgery, the fresh suture line in the mouth is a risk for infection or fistula. Attention to meticulous closure can only do so much. The diet of the immediate postoperative patient should remain soft to avoid chewing on the flap pedicle and limit the risk of trauma to the new sutures, with many surgeons choosing to NPO status for a week following surgery, with feeding tube nutrition. Many surgeons provide bite blocks for the patient to use for a few days to a few weeks postoperatively. Antibiotics are provided typically due to the resection portion of surgery. Complication rate is higher in cases that are done for secondary reconstruction (37.5 vs. 20%) and in T3 or T4 versus T1 or T2 tumors (44 vs. 18%) in Ayad et al.9,10

Pearls
- Good choice for small-to-medium–sized defects of the lateral pharynx and soft palate.
- Advantage of superior or inferior pedicle.
- Bilateral FAMM may be necessary to aid in tissue volume repletion and prevent VPI.
- Attention to postoperative course should include prevention of dentate patient biting down on the flap pedicle.
8.6.3 Buccal Fat Flap

The buccal fat was described in 1727 and refined in its description to include as a flap for use in oroantral communications by Egedy in 1977.\textsuperscript{10} Indications have expanded to include use for resurfacing of bony exposures of the mandible and maxilla, or for mucosal or myomucosal defects of the oral cavity and oro-pharynx. Rassekh et al reported (in a poster presentation) the use of buccal fat flaps in the reconstruction of soft palate defects from TORS with favorable results in small-to-medium-sized resections. Types I or II defects may be amenable to this type of reconstruction, typically in conjunction with Gehanno’s pharyngoplasty closure of posterior pharyngeal wall to remaining soft palate. Typically, the flap is pedicled on branches from the deep temporal and maxillary artery, transverse facial branch of superficial temporal artery, and facial artery branches. The buccal fat pad can consist of three to four processes of fat that result in a long axial pattern blood supply to the flap allowing for mucosalization within 3 to 4 weeks.\textsuperscript{11}

Patient Selection

Small-to-medium-sized defects of the lateral pharyngeal wall or palate are amenable to buccal fat flap repair. Larger through-and-through defects are not advisable due to the frailty of the buccal fat when placed under high amount of tension. Generally, the types I and II defects may allow for repair with this flap, and the author prefers to use it in cases with less than one-third loss of soft palate. If patients already suffer from trismus, the buccal flap has been reported to cause the same.

Perioperative Management

Given the recent resection, patients generally are not cleared for full diet. If no communication has been created to the neck, a soft or liquid diet may be initiated. Ideally, mucosalization will begin before solid foods are introduced and some patients will require feeding tube support for discomfort and nutritional support. A bite block can help prevent dentate patients from biting down on the flap pedicle. Patients should be initially discouraged from wide oral opening to avoid pulling the flap away from its suture line. However, after the flap has fully healed, range-of-motion exercises should be encouraged to prevent the aforementioned trismus. Small dehiscences may occur and these can be observed since mucosalizing flap may allow for healing to fill the defect and close it.

Surgical Technique and Considerations

The buccal flap is readily harvested with little need to extend incisions. The defect at the lateral pharynx typically created with resections in this area allows for dissection and rotation of the flap. The mucosa over the retromolar trigone, extending superiorly toward the maxilla is elevated. The buccal flap lies deep to the buccinator muscle, and careful dissection through the muscle is performed. Once through the muscle the fat will bulge into the dissection field. Fascia encases the flap and blunt dissection of the fascia off of the fat lobes will release it from the buccal space. Proximal pedicle will be visualized and care must be taken not to injure arteries and veins entering the axial flap here. The flap can then be freely rotated to cover lateral pharynx of soft palate defects. The flap is sutured to the surround mucosa with Vicryl or chronic suture in circumferential fashion until adherent (\textsuperscript{11}Fig. 8.8).
Reconstruction of the Lateral Pharynx and Soft Palate

Pearls

- Useful in types I or II defects of the soft palate or lateral pharynx.
- Typically used in combination with pharyngoplasty of soft palate and posterior pharyngeal wall.
- Axial flap can be pedicled to reach as far as contralateral superior tonsil.
- Minor dehiscence can be observed and may heal spontaneously.
- Bite block and soft diet until fully healed.

8.7 Regional Flaps

8.7.1 Temporoparietal Fascia Flap

The temporoparietal fascia (TPF) flap is a useful rotational flap for a variety of locoregional defects in the head and neck. It is an axial pattern flap consisting of fascia and potentially hair-bearing skin of the parietal scalp. If incision is made in the hairline, it can be well hidden. It produces thin tissues that can line defects in the ear, scalp, forehead, or pharyngeal subsites requiring soft tissue coverage. The flap can reach to the nasopharynx, and to the pharynx including the soft palate and lateral pharyngeal wall. It can provide a covering for exposed carotid in the pharynx and rebuild smaller defects of the soft palate and lateral pharyngeal wall. Pinto et al demonstrated a consistent blood supply and ready ability to tunnel the flap to the neck or pharynx, under or over the facial nerve.12

Patient Selection

A pharyngeal reconstruction encompassing less than one-half of soft palate, or of lateral pharyngeal wall alone is suitable case for TPF reconstruction. In general, deeper resections that involve pterygoid muscle, or more of the parapharyngeal space will not have enough filler tissue from TPF, thus patients requiring mostly mucosal reconstruction or mucosa and constrictor are best suited.

Surgical Technique and Considerations

The TPF flap is harvested via a curvilinear or “Y”-shaped incision in the parietal scalp extending from the helical root to the temporal line. Dissection through skin and subcutaneous fat is performed until the thin fascia is encountered. The layer is thin, and care must be taken not to cut through the blood supply or flap. The temporal fascia lies deep to this layer and if encountered indicates that the incision has been too deep. The pedicle is identified in the preauricular incision and the pedicle splits as it extends more distally. The facial nerve is intricately associated with the flap as it crosses the zygoma toward the frontal musculature. As the dissection proceeds inferiortly, the flap is narrowed on its pedicle toward the posterior third of zygoma to avoid the facial nerve course. To gain extra length on the flap, the pedicle can be dissected down to the external auditory canal height. The flap then must be tunneled to the pharynx for use of reconstruction. It has been the author’s practice to do a coronoidectomy then tunnel the flap inferior to the zygoma and posterior to the maxilla into the pharynx. A red rubber catheter is passed from oropharynx out to the preauricular incision via tunneled instrument. The distal TPF flap is sewn to the catheter and the catheter is pulled through the created opening and into the pharynx. The flap can then be sutured into the surrounding mucosal defect.

Note

It has been the author’s practice to do a coronoidectomy then tunnel the flap inferior to the zygoma and posterior to the maxilla into the pharynx.

Perioperative Management

General pharyngeal reconstruction protocol can be employed as above for other flaps. The donor site is closed in layered fashion with a small suction drain to prevent ecchymosis along the face.

Pearls

- Useful in types I or II defects of the soft palate or lateral pharynx.
- Axial flap can be pedicled and reach as far as contralateral superior tonsil.
- Minor dehiscence can be observed and may heal spontaneously.
- Bite block and soft diet until fully healed.
- Facial nerve courses over zygoma within the TPF layer—care must be taken to stay posterior to the frontal and zygomatic branches.

8.7.2 Submental Island Flap

The submental island flap is a useful local option primarily in oral reconstruction, or skin and soft tissue defects of the neck, face, parotid, malar skin, and also pharyngeal axis. It can be large and long enough to reach contralateral pharynx (up to 18 cm in length and 7 cm in width). It provides skin and subcutaneous fat, with proximal muscle of the anterior digastric belly and mylohyoid, if needed. It allows for primary closure of the donor site and is often easily incorporated into a neck dissection incision already required for resection. The flap can easily be tunneled via a lateral pharyngotomy that is either already created or easy to establish. The more distal aspects of the flap are at highest risk for poor blood supply in this axial flap as it will be furthest from the submental branches of the facial artery. Although the flap can be harvested when an ipsilateral neck dissection is required, the removal of level I lymph nodes puts the small branches supplying the flap at risk as they are removed. Though thin, the flap can be made longer than the skin requirement and de-epithelialized to provide additional bulk to bury in the parapharyngeal space if desirable. The flap can reconstruct nearly any lateral pharyngeal defect and most palate defects up to types III and IV in nature due to the large volume of tissue available.13
**Patient Selection**
Types I to IV defects are all candidates for reconstruction with this flap. It can seal the neck from the oropharynx and provide palate reconstruction readily. It can be used in similar fashion to the radial forearm flap and is therefore of use in most defects but particularly in the larger defects such as types III or IV.14

**Surgical Technique and Considerations**
The skin paddle is marked according to desired volume of skin and soft tissues. The incision is made through skin and platysma and these layers are raised from distal to proximal until the anterior belly of digastric is encountered. The majority of vessels run deep to the muscle belly so the muscle is incorporated into the flap by dividing its attachments to mentum and at the tendon. The flap is then proximally elevated back to the submandibular gland and the branches to the flap can now be visualized. If neck dissection is required, these branches are carefully preserved. The submental artery and veins drain into the facial vessels. Additional length can be acquired by dissecting the facial vessels more extensively to create a greater range of motion. The flap is then tunneled into the oropharynx and sutured into place of the defect (Fig. 8.9).

**Perioperative Management**
Similar to aforementioned protocols, pharyngeal postoperative care includes close monitoring of the flap and pharyngeal rest for 1 week in nonradiated patients, and potentially longer for radiated patients. The submental flap incision is treated like any other neck incision with drains as appropriate and closed as neck incision would be.

**Pearls**
- Useful in types I to IV defects of the soft palate or lateral pharynx.
- Axial flap can be pedicled and reach as far as contralateral superior tonsil.
- Bite block and soft diet until fully healed.
- Distal flap at greater risk of necrosis, so consider cutting back on flap to ensure distal skin has good venous drainage.
- Harvest digastric anterior belly with flap on ipsilateral side to avoid damage to submental vessels.

**8.7.3 Regional Muscle Flaps (Temporalis, Sternocleidomastoid, Digastric, Strap Muscles)**
Muscles in the region of the pharynx can be used as adjunctive and supportive measures for underlying repairs that may be tenuous. Regional muscles such as digastric, straps, sternocleidomastoid (SCM), or temporalis can be rotated into the lateral pharynx, and have mostly been used by the author as second layers of closure often when tenuous primary closures exist, or in cases of postradiation reconstructions. They are limited by the arc of rotation and size of the muscle but can supply the added security of an additional layer of closure.

**Note**
Regional muscles such as digastric, straps, SCM, or temporalis can be rotated into the lateral pharynx as a primary or second layer closure.

**Patient Selection**
Postradiated patients may benefit from second layer closures using rotated muscle.

**Surgical Technique and Considerations**
Each muscle is supplied by a unique blood supply that can be used to pedicle the muscle and rotate. The SCM has superior supply from the occipital vessels. Therefore a superiorly based flap can be rotated into the pharyngeal area while preserving the 11th cranial nerve. The temporalis is less useful due to limited reach but can be released from temporal line through a similar incision to TPF flap and tunneled in the same fashion to supply muscle bulk to lateral pharynx based on the deep temporal artery and vein. Strap muscles are supplied by ipsilateral superior thyroid branches and can be dissected and rotated on this blood supply. Lastly, the digastric anterior belly can be detached from the mentum and maintained on the submental branches that course nearby and are used with submental island flaps.

**Pearls**
- Useful in types I and II defects or as secondary layer of closure.
- Axial muscle flaps.
- Bite block and soft diet until fully healed.
- Typically, not used as primary closure layer, but useful in tenuous or at-risk pharyngeal closures such as those done after radiation or salvage situations.

**8.7.4 Radial Forearm Free Flap and Ulnar Free Flap**
The radial forearm and ulnar flap have similar attributes and are therefore included together here. Both provide variable amounts of skin and are versatile flaps that can provide reconstruction of a wide variety of oropharyngeal and other defects.

The radial forearm free flap (RFFF) has been considered a "workhorse" flap in head and neck reconstruction due to the ability to harvest quickly, with good size vessels, and high...
degree of success. The flap has been in existence for over three decades since its first use by the Chinese in 1978, and within several years, the utility of the flap extended to Europe and was utilized for nasal reconstruction and intraoral defects.

The RFFF is based on the septocutaneous perforators of the radial artery, whereas the ulnar flap is based on similar perforators from the ulnar artery and veins. It has been used in nearly every type of head and neck reconstruction, and can be templated to create enough tissue for even large defects of the oropharynx. The pliable and typically thin nature of the forearm flap help in the inset into small access defects such as TORS pharyngeal defects.

Fig. 8.9 (a) Design of a left-sided pedicle flap showing size of flap available is similar to that achieved with a forearm. (b) Elevation of the submental flap. (c) The flap is pliable and easily provides enough length to reach the palate and base of tongue. (d) Inset of submental flap provides bulk and coverage of base of tongue and palate defects.
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Surgical Technique and Considerations

To harvest, the arm is laid supine and abducted. A skin paddle is outlined overlying the radial or ulnar artery and of a size specific to the required reconstruction. One may choose to harvest with or without the aid of a tourniquet depending on surgeon preference. In elevation of fascia, paratenon is identified and preserved. The paratenon supplies a minimal vascularity to the skin graft that will later close the donor bed.

The pedicle, which is comprised of the radial or ulnar artery and two venae comitantes is identified in the intermuscular septum between the brachioradialis and the flexor carpi radialis in the case of the radial forearm flap, and directly deep to the skin of the ulnar forearm in the case of the ulnar flap. It is helpful in the ulnar harvest to ultrasound the artery to delineate the direction of the pedicle. As the pedicle is followed proximally in either flap harvest, attention to location of the radial and ulnar nerves (more so for the ulnar flap) should be taken to carefully preserve the nerves. The superficial venous drainage systems can be harvested in both flaps, though more reliably in the radial forearm flap. In addition, the medial or lateral antebrachial nerves can be identified and preserved for anastomosis and creation of a “sensate flap” if they supply the skin of the forearm design adequately.

The donor bed skin edges can be partially brought together to reduce the size of the defect, and, most commonly, a split-thickness skin graft from the thigh is harvested and placed to repair the remaining defect—though multiple options are available. A dorsal splint is placed for 5 days to immobilize the wrist and maximize skin graft take.16,17

The flap can then be transferred to the head and neck to perform reconstruction. Much has been learned in the early insets performed—a large portion of the flap inset can take place transcervically. A typical defect comes down to the vallecula and therefore the lateral pharyngotomy provides access to the base of tongue and posterior pharyngeal wall. The first few sutures are used to primarily close the pharyngeal wall to the base of tongue in a maneuver that narrows the resected side and diverts food to the sensate and nonoperated side. The “heart-shaped” flap design then allows the apex to inset into the lower pharynx and base of tongue to prevent tongue contracture or motion limitation. The final inset is then done transorally with a bilobed (upper heart shape allows double layering) flap to sew to both the nasal and oral sides of the soft palate. This allows additional bulk to prevent VPI (> Fig. 8.10).

Perioperative Management

Similar to those described in previous flaps. Additional management of the arm and skin graft to arm with immobilization and bolster placement.

Pearls

- Useful in types I to IV defects.
- Versatile flap with ability to modify and deal with any defect.
- Bite block and soft diet until fully healed.
- Simultaneous harvest while resection takes place.
- Transcervical inset of lower portion and transoral of palate portion.

8.7.5 Anterolateral Thigh Flap

The anterolateral thigh flap (ALTF) is a well-described perforator or musculocutaneous free flap arising from the descending branch of the lateral circumflex femoral artery and vein. The flap can be harvested as a two-team flap and has the capacity to be as large as 25 × 15 cm. It was first described by Song in 198418 and has been popularized in head and neck reconstruction by Wei and Chana19 due to its flexibility. The flap consists of skin and subcutaneous fat, tensor fascia, and variable amounts of muscle pending perforator course (80% are transmuscular, 20% septocutaneous), and whether the flap is harvested as perforator or with muscle.20 The flap has the major advantage of being able to handle almost any size defect in the lateral pharynx or palate, including total palate, and lateral pharyngeal defects at the same time. It has a long and large caliber pedicle useful in anastomosis. It can additionally provide bulk for the parapharyngeal space and allow for bulkier reconstruction that is favorable in large defects of this region. The very bulk that is helpful to divert food and prevent VPI also limits the inset of the flap. Larger, thicker thigh flaps are difficult to inset purely transcervically or transorally. Therefore, unless the thigh is thin and inset similarly to the forearm flaps, a lip split and jaw split is greatly helpful in access to the area for reconstruction.15

Note

The bulk associated with the ALTF is helpful to divert food and prevent VPI, however, it also makes the flap inset a challenge.

Patient Selection

Large types III and IV defects with substantial loss of parapharyngeal space contents, neck contents, and those with prior treatment are the best candidates for ALTFs for pharynx and palate. The ALTF is large enough that it makes most practical sense to use it for large defects. Previously radiated patients and salvage surgery are two situations that benefit from transfer of larger-volume free tissue. In many of these cases, open approaches are used to compliment transoral approaches, supplying the space needed to inset the flap properly. The end goal
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Fig. 8.10 Resection of large oropharyngeal tumor with transoral robotic surgery (TORS) and transcervical approach, followed by reconstruction with ALT free flap. (a) Delivery of tumor transcervically after superior cuts made robotically. (b) Typical view from transoral following superior cuts. (c) Tumor excised shows the extent and size of resection. (d) Forearm flap with initial inset of apex of flap into vallecula after partial closure (note skin graft harvested from forearm paddle before flap harvest). (e) Transoral exposure for the palate and posterior floor of mouth inset after inset of lower portion transcervically.
in using the ALTF is to provide a bulky reconstruction that will divert food to the senate side of the pharynx during swallowing and close the defect while providing additional tissue behind the suture line (subcutaneous fat and muscle), in cases where wound dehiscence or complication are more common.

A second use of the ALTF is in thin or cachectic patients with smaller defects that the ALTF can be used much the same as forearm flaps would be. These are effective for types I and II defects in which multilayer palate reconstruction and lateral pharynx reconstruction are necessary.

**Surgical Technique and Considerations**

The ALTF and its harvest have been well described in the literature. The perforators are concentrated along a line connecting the anterior superior iliac crest and lateral patella. The highest concentration lies in the middle third of this line with 85% or more occurring in this location. The handheld Doppler can be used to localize perforators and ensure the incision is appropriate. The separation between vastus lateralis and rectus femoris can be palpated as a second confirmation of the location of the pedicle.
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An anterior incision is made and the skin, subcutaneous fat, and tensor fascia are divided, exposing the rectus muscle. Occasional perforators will be seen transgressing the rectus. They can be harvested but must be traced through the muscle, and typically additional perforators through vastus will be seen used. The rectus is reflected medially and dissected down to the vastus medialis and fascia overlying it. The skin is reflected laterally and the main pedicle is visualized. The skin is then dissected until the perforators are seen entering the skin paddle. The perforators can vary in angle of entry, depth of muscle of vastus lateralis they traverse, and number present. At least presence of one perforator of adequate size is enough to proceed.

The posterior incision is then made and dissection down to the rectus lateralis is performed. The skin paddle is now detached from surrounding skin and can be checked for bleeding. Posterior dissection to visualize the perforators is now helpful to delineate their course. Depending on tissue needs the perforators can now be dissected through muscle as a perforator flap or a cuff of muscle harvested if useful in reconstruction. The nerve to the vastus lateralis courses along the pedicle and typically be preserved, but its sacrifice does not result in significant functional consequence—thus compromise of the pedicle should not be risked when the nerve is not easily dissected off of pedicle. The flap can now be raised from distal to proximal while clipping the distal pedicle and perforators to the vastus intermedius and lateralis. The proximal pedicle is dissected until the rectus branches are visualized and preserved.

The flap can be modified to create a “butterfly shaped flap” to maximize the mobility of each individual limb of the flap for better tongue and palate mobility. The author has employed this technique with success in recurrence or large defects of the pharynx and palate. In a series of 45 patients presented at the Combined Otolaryngology Sections Meeting in 2013, the flap was successful in decannulation (44) and peg removal (40) in a majority of T3 and T4 cancer resections. In addition, modification to the flap harvest can allow for bony reconstruction in the event of bone resection (> Fig. 8.11).21

The donor site can be closed primarily in the majority of cases. Inset requires closure of flap to mucosa with absorbable suture. The goal of inset is to close all mucosal defect to flap skin for the pharynx, and to perform pharyngoplasty with flap to soft palate, thereby obliterating the nasopharynx and palate space.

Perioperative Management

Similar to aforementioned protocols, pharyngeal postoperative care includes close monitoring of the flap and pharyngeal rest for 1 week in nonirradiated patients and potentially longer for irradiated. The ALTF incision is treated like any other neck incision with drapes as appropriate and closed as neck incision would be. The thigh is drained with suction drain until output is low enough for removal.

Pearls

- Useful in types I to IV defects.
- Versatile flap with ability to modify and deal with any defect.
- Bite block and soft diet until fully healed.
- Simultaneous harvest while resection takes place.

8.8 Conclusion

Oropharyngeal defects present a challenge to the reconstructive surgeon. There are many tools available in the local, regional, and free tissue arena to help heal these patients, and care should be taken to ensure the inset aids in the function of the pharynx. This chapter and examples can serve as a template for the use in reconstruction of the pharynx, but in no way is exclusive. Ultimately, surgeons will choose the reconstructions that work best in their hands and give reproducible and safe results.

References

9 Carcinoma Involving the Mandibular Alveolus and Retromolar Trigone

Tjoson Tjoa and Derrick T. Lin

9.1 Introduction

Cancers of the oral cavity are estimated to affect over 30,000 people in the United States each year.1 The oral cavity can be divided into seven subsites, which include the lips, tongue, floor of mouth, hard palate, buccal mucosa, retromolar trigone (RMT), and alveolar ridges. Although cancers of the oral cavity are often grouped together, they represent a diverse group of tumors, with each subsite possessing its own tumor biology and patterns of local extension. The RMT and the mandibular alveolus are two unique anatomical areas, characterized by their close proximity to the mandibular cortical bone. This imparts distinctive behavior on cancers of this area, and treatment decisions are often centered around the presence or absence of bony involvement. Because they account for a small percentage of oral cavity tumors and are relatively rare, no randomized controlled trials have been performed on RMT and mandibular alveolus cancers, and optimal management of tumors in this area is an ongoing topic of debate. This chapter encompasses a review of the anatomy, presentation, workup, and treatment modalities of these two unique oral cavity subsites.

9.2 Anatomy

The mandible is the largest and strongest bone of the facial skeleton. It consists of a curved, horizontal portion, the body, and two perpendicular portions, the rami, which meet the lateral ends of the body at nearly right angles.2 The superior surface of the mandibular body containing the tooth sockets is considered the mandibular alveolus (▶ Fig. 9.1). The RMT refers to the triangular area of mucosa immediately posterior to the mandibular alveolus, overlying the ascending ramus and attached muscles of mastication.2,3 An early anatomical definition of the RMT was provided by Barbosa, who initially described a surgical technique for resection of cancers in this area.4 The term was used to designate “the part of the buccal cavity that lies between two dental arcades on either side and behind roots of last molar teeth.”4

The medial border of the RMT is the temporal crest and its lateral border is the anterior border of the ramus. Its base is the gingiva posterior to the third molar, and its apex is a thickened area of mucosa at the maxillary tuberosity cranially.5,6 In the majority of instances, the medial limit of the RMT is marked by fold of mucosa caused by prominence of the pterygomandibular ligament4 (▶ Fig. 9.2). The retromolar mucosa receives a sensory supply primarily through the buccal branch of the trigeminal nerve, while a limited portion of the floor of the mouth, anterior pillar, and tongue is innervated by the lingual nerve. The arterial supply comes principally from branches of the internal maxillary and facial arteries. The veins are tributaries of the internal jugular and of neighboring venous plexuses, especially the internal pterygoid plexus.7 The main lymphatic drainage of the RMT is to the deep jugular chain lymph nodes in level II, with minor drainage into the periparotid and retropharyngeal nodes.6 The mandibular alveolus has been found to drain predominantly to levels I and II along the deep jugular chain.7,8

Note

The main lymphatic drainage of the retromolar trigone is the jugular chain lymph nodes in level II, with minor drainage into the periparotid and retropharyngeal node. The mandibular alveolus drains predominantly to levels I and II along the deep jugular chain.

The RMT mucosa is directly contiguous with the buccal mucosa laterally, the anterior tonsillar pillar and soft palate medially, and the gingival mucosa of the upper and lower alveolar ridges.3,9,10 Its proximity to these structures, combined with the propensity of RMT tumors to initially spread superficially to surrounding areas, has resulted in several reports within the literature grouping tumors of the RMT with those of the soft palate, anterior tonsillar pillar, and buccal mucosa.11,12,13 However, it is important to consider tumors that arise from the RMT and mandibular alveolus as distinct entities from those of the buccal mucosa and oropharynx. Along the alveolus and RMT, the mucosa is closely approximated and tightly adherent to the mandibular periosteum and bone, which can act as a barrier to tumor spread.8,9 Thus, cancers of this area tend to have a different growth pattern and a higher propensity for bony involvement than those of other subsites in the oral cavity and oropharynx.
Along the alveolus and retromolar trigone, the mucosa is densely adherent to the mandibular periosteum and bone. Cancers of this area have a higher propensity for bony invasion than those of other subsites in the oral cavity and oropharynx.

9.3 Clinical Features

9.3.1 Etiology

Oral cancer is the sixth most common cancer worldwide and is among the 10 top causes of cancer death in the world. Squamous cell carcinoma (SCC) accounts for over 90% of these, and is the most common cancer to affect all subsites, including the mandibular alveolus and RMT. Retrospective case series and database studies have reported RMT cancers to account for 5 to 10%, and mandibular alveolar cancers to comprise 6 to 10% of all oral cavity cancers in the United States. For alveolar ridge carcinomas, incidence may be higher in certain populations, for example, with carcinomas of the mandibular alveolar ridge accounting for 30% of oral cavity cancers in a 10-year retrospective study out of Japan and accounting for 9% of all cancers in South India.

While the etiology of retromolar trigone and alveolar cancers is multifactorial, the traditional risk factors for oral cavity SCC, particularly tobacco, alcohol, and betel nut usage, have been associated with these subsites. Particularly with RMT cancers, up to 78 to 86% of patients in larger series have been documented to have a history of either tobacco or alcohol, or a combination of the two. With regard to lower alveolar cancers, the association with these risk factors is present, but less strong. In a study of 61 patients out of MD Anderson, Byers et al found that less than 50% had a history of tobacco and alcohol usage, but that in over 55%, chronic irritation by ill-fitting dental appliances may have been a contributing factor.

9.3.2 Presentation

Tumors of the RMT typically present with pain, which can be accentuated upon mouth opening. Trismus and referred otalgia are also often present upon presentation, up to 52% of the time in some studies. Because of the location of RMT, the tumor has relatively easy access into the masseteric and pre-styloïd parapharyngeal space, and can infiltrate into the masseter and medial pterygoid muscles. While the presence of trismus suggests pterygoid invasion, it may also be the result of inflammation in the surrounding musculature and not necessarily direct extension of tumor into the pterygoids. Invasion of the buccal, lingual, and inferior alveolar branches of the mandibular nerve can also result in trismus. Other symptoms on presentation include ulceration, bleeding, weight loss, and external swelling. Anesthesia of the lower lip can result from invasion of the mental nerve.

Alveolar ridge cancers can present with all of these symptoms as well, with pain and ulceration being most common, and trismus less common. Ill-fitting dentures, mobile teeth, and nonhealing dental extraction wounds have also been present at the time of diagnosis. The mandibular alveolar ridge, posterior to the bicuspid teeth, is the most common site of these.
lesions. While duration of symptoms prior to diagnosis is approximately 5 months for RMT lesions, it can be longer in alveolar ridge lesions due to the diverse clinical appearance and many benign lesions that may mimic carcinoma, including lichen planus, periodontal disease, and nonspecific granulation tissue. Thus, patients can live with lesions for years prior to the diagnosis of cancer.

A unique feature of cancers of the RMT and alveolar ridge is their growth pattern, largely dictated by their proximity to the mandibular cortical bone. Unlike tumors surrounded by soft tissue, which can grow radially, cancer growth in these areas is initially limited into deeper planes by periosteum and bone. Consequently, tumors of the gingiva of the RMT and alveolar ridges tend to spread superficially during their initial growth phase and there are proportionately fewer cells than in cancers that can grow spherically. As Barker said, “The stage according to the diameter of lesion is not a reflection of the volume of the cancer.”

Note
Tumors of the gingiva of the RMT and alveolar ridges tend to spread superficially during their initial growth phase and there are proportionately fewer cells than in cancers that can grow spherically. Therefore, the stage according to the diameter of lesion is not a reflection of the volume of the cancer.

The overall incidence of mandibular bone invasion based on studies with histopathologic confirmation is 10 to 48% in RMT lesions and 36 to 88% in alveolar ridge lesions. RMT lesions can invade the maxilla superiorly as well, at a rate equivalent to slightly lower (12–22%) than the mandible. While early studies postulated that bony invasion by SCC was resulted from the involvement of lymphatics within the
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periosteum, it is now clear that mandibular invasion occurs predominantly via direct infiltration of tumor through the alveolar ridge or lingual cortical bone. Histopathologic studies of the interface between bone and tumor have revealed that the site of tumor entry into the mandible is entirely dependent on the location of the tumor in relation to the mandible. For alveolar ridge tumors, this is often the alveolar crest, and for RMT tumors, this is often the lingual mandibular cortex. Other less common routes of entry include via the mental and mandibular canals in advanced-stage tumors, and the inferior border of the mandible by cervical lymph nodes. Regardless, a high suspicion of mandibular bone involvement is necessary for these tumors, particular with alveolar ridge involvement.

9.3.3 Staging

Staging of the primary lesion in RMT and alveolar ridge cancers is based on the AJCC TNM staging system (Table 9.1). As with other oral cavity cancers, T4a lesions are those in which the tumor invades adjacent structures, including the extrinsic tongue musculature, facial skin, maxillary sinus, and through cortical bone. However, because of the pattern of initial superficial spread, and the high rate of bone involvement, it can be difficult to accurately stage these lesions on initial examination. Generally, T4 lesions are associated with worse local control. Additionally, bone invasion and masticator space extension have been established as unfavorable prognostic factors.

In fact, involvement of masticator space has been shown to be more relevant than T classification in terms of overall survival. This may be due to the fact that small lesions with minimal foci of osseous invasion can be understaged on initial evaluation, thus resulting in erroneous local control rates for any given stage (Table 9.1).

Regarding nodal metastases, the most common areas of clinical involvement for both alveolar ridge and RMT carcinomas are along the ipsilateral submandibular area and superior jugular chain, involving levels I, II, and III. Clinically positive nodes at presentation are relatively infrequent, reported at anywhere from 5 to 36% in RMT cancers and 16 to 21% in alveolar ridge. However, the development of pathologic nodes along the course of treatment has been reported to be much higher, from 26 to 88%, and N stage is known to be a significant negative prognostic factor. Rarely, contralateral nodes are found to be involved at the time of initial surgery.

9.4 Preoperative Assessment of Bone

Given that bony invasion is common in these tumors, and T4 tumors are associated with worse local control, determining the presence and extent of bony involvement is critical in their management. Unfortunately, clinical evaluation has its limitations, and there is no single imaging technique that can accurately predict mandibular involvement in tumors of the RMT and alveolar ridge. Various studies have shown that anywhere from 33 to 50% of patients with histologically proven bone infiltration show no radiologic sign of bone invasion.

Evaluation begins with a detailed clinical examination with bimanual palpation and assessment of the mobility of the tumor in relation to the adjacent structures. Signs such as alveolar nerve anesthesia and bony irregularities can help reveal bony involvement, though neural involvement extensive enough to block transmission is uncommon. While some studies noted that clinical examination by an experienced
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clinician was more accurate than radiographic studies in predicting bone invasion.\(^3^4,^3^6\) A number of studies have demonstrated that clinical evaluation has a sensitivity ranging from 32 to 96%.\(^3^1,^3^7,^3^8\) Additionally, with pterygoid involvement or inflammation from RMT lesions, the ability to perform a detailed clinical examination can be limited.

Radiographically, orthopantomograms, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, and bone scans have been studied and found to have varying degrees of accuracy in detecting bony involvement.\(^3^1\) Panorex has been shown to have utility in determining the superior-inferior extent of tumor in bone, which is one of the most important factors influencing the selection between marginal and segmental mandibulectomy.\(^3^1,^3^3,^3^9\) Its use has been advocated as an initial imaging modality for alveolar ridge carcinoma. However, the panorex is not great at detecting early invasion of the mandible with less than 30% of mineral loss.

CT has become standard in the axial imaging of head and neck malignancy. Lane et al found that CT is most commonly used for radiographic staging, and although its specificity for bone involvement in SCC of the RMT is 91%, its sensitivity is low, at 50% (Fig. 9.5).\(^9\) The positive predictive value of CT in that study was 87.5%, but the negative predictive value was 61%, demonstrating that CT can be a reliable marker of bony invasion if it is detected, but is not a useful indicator if it is not detected.\(^4^0\) However, the CT technique used in this study was with thick 5-mm sections evaluated only in the axial plane. With the more recent 16-section multidetector CT, the sensitivity for mandibular cortical invasion has been demonstrated to be 94%, with 83% sensitivity at detecting marrow invasion.\(^4^1\) Unfortunately, dental amalgam can be limiting to CT analysis, and direct perineural spread into the mandibular and mental canals without bone erosion are not easily detectable with CT. Additionally, defects in the cortex secondary to tooth socket irregularities or periapical disease are detected by CT scan and can be mistaken for bone involvement.\(^4^2\)

Relative to CT scans, MRI scans offer superior resolution within the soft tissue and medullary space of the bone, and are less affected by dental amalgam artifact. Crecco et al compared MRI scans with pathologic data in a series of 22 patients with RMT cancers and reported a high accuracy of MRI to evaluate the T-stage and relationships between surrounding structures. The sensitivity of detecting bone marrow invasion was 100%.\(^4^3\) Other studies have corroborated the effectiveness of MRI in evaluating involvement of the medullary space of the mandible.\(^4^4,^4^5\) van den Brekel et al compared the panorex and CT with MRI in assessing tumor invasion of the mandible and found that MRI had the highest sensitivity, but the lowest specificity, and often overestimated the extent of tumor invasion.\(^4^6\)

Bone scintigraphy is a useful method that is sensitive to the increased bone turnover in cancers of the alveolar ridge and RMT, with the ability to detect periosteal involvement. It has been shown to have a sensitivity of 100% for detecting bone involvement. However, osteoblastic activity is high in osteomyelitis, fractures, and periodontal disease, which limits the specificity of bone scans. Positron emission tomography (PET) scans combined with CT scans can also be used as an adjunct, but rarely provide enough information as a stand-alone imaging modality to determine bony involvement. Most recommend a combination of CT with MRI, along with clinical and intraoperative assessment of the bone and periosteum, to determine involvement of bone along the RMT and mandibular alveolus.

9.5 Treatment

9.5.1 Modality

Because of the relative rarity of RMT and mandibular alveolus cancers, no prospective randomized trials have been performed, so no clear recommendations have been standardized in their treatment. SCCs of the RMT and mandibular alveolus have been treated with primary surgery, primary radiation, and with combinations of surgery, radiotherapy, and chemotherapy with varying success. The majority of publications favor primary surgical management, with or without radiation, though others have reported success with primary upfront radiation (Table 9.2 and Table 9.3). The National Comprehensive Cancer Network (NCCN) guidelines state that early disease can be treated with single-modality therapy, either surgery or radiation, and that advanced disease should be treated with multimodality therapy.
In the earliest publication, comparing surgery to radiation in the treatment of RMT cancers, Byers et al reported their experience at MD Anderson with 110 patients treated initially either with surgery, radiation, or a combination of the two modalities. It included patients of all stages. The conclusion was that single-modality therapy was equivalent to combined-modality treatment. Similarly, Binahmed et al noted no significant difference in 5-year overall survival rates within a group of 76 patients with RMT cancer treated with either surgery, radiation, or a combination of the two.

Several studies, however, have shown a significant benefit to multimodality therapy. Huang et al reviewed a series of 65 patients with early- and late-stage RMT disease and found that surgery plus radiation had a significant impact on disease-free survival and locoregional control. In particular, the locoregional recurrence rate was 18% after combined-modality treatment, whereas the locoregional recurrence rate was 54% after radiation alone. Similarly, Mendenhall et al reviewed a series of 99 patients treated with surgery and radiation or definitive radiation alone. Multivariate analysis revealed that the likelihood...
of cure was better with surgery and radiotherapy compared with definitive radiotherapy. This was found to be true for local control, locoregional control, cause-specific survival, and overall survival. Most recently, Hitchcock et al reviewed 110 patients with RMT carcinoma and found a 69% 5-year locoregional control rate when surgery and radiation were used, versus 50% for radiation alone.48

Note
Multivariate analysis has revealed treatment of RMT tumors with surgery and radiotherapy is optimal when compared with definitive radiotherapy alone.

Similarly, series examining single and bimodality treatment for mandibular alveolar ridge cancers have demonstrated that surgery with postoperative radiation is most effective for both early- and advanced-stage lesions.17,20,35,47

Consistent with prior studies that demonstrated margin status and regional nodal status to be prognostic factors, Mendehall et al found that patients with positive margins and extracapsular extension were found to have a poorer prognosis, and Huang et al showed that nodal status significantly affects the rate of distant metastasis and decreases disease-free survival.21,28

Note
Patients with positive margins and extracapsular extension have been found to have the poorest prognosis.

Common complications of treatment include osteoradionecrosis, fistula formation, bone exposure requiring surgical treatment, infection, and permanent gastrostomy tube dependence.48 As expected, the probability of severe complications, such as osteoradionecrosis, was higher with primary or postoperative radiation than with surgery alone.21 Overall, upfront surgery with radiation is the most commonly used treatment method for mandibular alveolus and RMT cancers. Concurrent postoperative chemoradiation is advocated for advanced-stage tumors and those with poor histopathologic prognostic features. Combined upfront chemoradiation treatment is scarcely described, typically reserved for patients who are poor surgical candidates without documented bony involvement.

9.5.2 Surgical Treatment
Classically described surgical approaches to the RMT and mandibular alveolus have traditionally been aggressive, due to the high propensity of bony involvement. Approaches to the retromolar trigone are similar to approaches for oropharyngeal primaries, due to the frequent involvement of the soft palate and tonsillar fossa mucosa. Transoral approaches are typically reserved for smaller T1 and T2 lesions that are easily accessible and with limited oropharyngeal extension (Fig. 9.6a). Upper or lower cheek flap approaches can be useful for posteriorly located tumors (Fig. 9.6b). A lip-split and midline mandibulotomy is a useful approach to expose RMT tumors in which trismus limits access (Fig. 9.6c). While location and size of each tumor help determine the best approach, the central question that ultimately dictates the approach and extent of resection for advanced-stage lesions is whether the bone is involved, and if so, whether a marginal or segmental mandibulectomy is indicated. The extent of bony resection has been an evolving area of controversy, and a standard of care has yet to be established.

Barbosa in 1959 described what came to be known as “the retromolar operation,” which consisted of removing, together with the RMT mucosa, all the neighboring regions customarily invaded by the tumor. This included the masseteric region, the prestyloid part of the zygomatic fossa, the superior maxillary tuberosity, ascending ramus of the mandible, and the posterior part of the horizontal ramus. These structures were removed in one block if possible. In a small series of patients, this operation was shown to be an effective treatment for RMT carcinomas.4 The approach to this operation can be achieved through a transoral approach (Fig. 9.7) or through a transcervical approach (Fig. 9.8).

In 1993, Kowalski et al described an extended version of the retromolar operation in a series of 114 patients, calling it the extended commando operation. This included a lower lip-split incision with segmental mandibulectomy, along with the opening and disjointing of the temporomandibular joint (TMJ). Most patients in this series were closed primarily. The local control rate was found to be 73%. The most frequent complications in this study were local infection, wound dehiscence, and flap necrosis.18

Recently, Deo et al reviewed stages III and IV RMT cancers that were treated with radical surgery and postoperative radiation. The surgery involved a lip-split incision, with apron extension to neck in order to resect the primary tumor with 1-cm margins and en bloc hemimandibulectomy. A maxillary alveolectomy was performed if the tumor involved the upper alveolus. Infratemporal fossa clearance was established via en bloc resection of the pterygoid muscles, inferior alveolar nerve, and pterygoid plexus. A pedicled pectoralis major flap and titanium plate were used to reconstruct the defects, and all patients received postoperative radiation. The 3-year overall survival rate was 71%, and the authors recommended hemimandibulectomy in all locally advanced RMT tumors.15

More recently, the necessity of wide bony resection margins has come into question. Despite improvement in functional oromandibular reconstruction, segmental mandibulectomy defects remain a source of functional and sometimes cosmetic difficulty for patients.31 Additionally, the use of free tissue transfer for bony reconstruction requires significantly more health care resources than the simpler reconstructions that marginal mandibulectomy requires.

Note
In select cases, a marginal mandibulectomy may be appropriate. For tumors that do not invade the marrow space, this approach is associated with a better functional outcome than a segmental mandibulectomy.
Marginal mandibulectomy was initially described in 1923 by Crile as an incision that is carried down to the bone so that a slice of bone can be split off in one piece, bearing the undisturbed cancer off as on a bone platter (Fig. 9.9a, b). Greer popularized the technique in 1953, and it has since been used typically to describe resections of either the inner table or alveolar ridge of the mandible, often in the setting of floor of mouth or tongue cancers where the tumor abuts the mandible but does not invade it clinically. Beginning with Byers et al in 1981 and Wald and Calcaterra in 1983, both mandibular alveolar and RMT carcinomas have been shown to have similar response rates when treated with marginal versus segmental mandibulectomy.

Totsuka et al performed clinicopathologic studies with cancers of the mandibular alveolus and found two distinct patterns of involvement: an infiltrative pattern and an expansive pattern. Infiltrative tumors tend to invade the mandible through defects of the cortical bone or periodontal space, or directly by destroying the bone. In expansive lesions, bone is eroded in a generally smooth or slightly concave manner, with
no tumor invasion in relation to the periodontal space, the neurovascular canals, the inferior alveolar nerve, or the periosteum. In addition, there is always a small amount of connective tissue between the tumor tissue and the eroded surface of the bone. Thus, in the expansive pattern of bone involvement, the tumor seems to invade the mandible in proportion to the resorption of the bone, whereas in the infiltrative pattern the tumor tends to invade the mandible through spaces or aggressively by destroying the bone. Based on this information, marginal mandibulectomy was selectively applied to expansive bone defects that do not extend beyond the inferior alveolar canal and to invasive bony lesions confined to the superficial alveolus. With a 2-year follow-up, Totsuka et al reported similar survival rates between marginal (86%) and segmental mandibulectomy (82%). Local control was slightly higher in the marginal group, and tumor recurred in soft tissue rather than bone in most cases.51

Petruzzelli et al reviewed patients treated with posterior marginal mandibulectomy for RMT carcinomas and found that in the absence of clinical or radiographic evidence of bone invasion, a posterior marginal mandibulectomy provides the necessary bony margin to prevent local recurrence, with local control rates above 90%.51 Pascoal et al in 2007 compared 20 patients with locally advanced RMT carcinoma, but no clinical or radiographic evidence of bony invasion, who underwent either marginal or segmental mandibulectomy with postoperative radiation, and found no difference in local and regional recurrence rates between the two. In fact, the survival rate of the groups treated by segmental mandibulectomy was lower than that of the marginal mandibulectomy group (45 vs. 55%). Since it does not improve the survival rate, and may come with additional morbidity, the recommendation was that segmental resection should not be advocated without preoperative evidence of bony invasion.51

Fig. 9.7 The transoral approach may provide adequate exposure to early-stage tumors.

Fig. 9.8 The transcervical approach provides exposure to the mandible in the event that a marginal mandibulectomy is necessary.
Pandey et al in 2009 showed that tumor stage, surgical margins, and nodal stage are predictors of survival in RMT carcinomas, and that there was no difference in survival between patients with pathologically positive mandibles and those without mandible involvement. Their conclusion was that conservative marginal resection of the bone may be carried out, even in presence of involved mandible, as long as negative resection margins can be achieved.52 Several other studies have shown similar locoregional control and survival rates with segmental and marginal mandibulectomy for both RMT and mandibular alveolus carcinomas.5,23,53,54

Unfortunately, all locoregional control and survival data are retrospectively gathered and subject to selection bias. Patients in all these studies were chosen for either a marginal or segmental mandibulectomy based on clinical suspicion of bone involvement and intraoperative assessment by very experienced surgeons. Segmental mandibulectomy (= Fig. 9.10a, b) is typically performed when the bone is clearly and extensively involved or to maintain an oncologically safe margin of soft tissue in deeply invading tumors.55 Periosteal stripping and frozen section analysis of cancellous bone can be used to guide management of the mandible, with high sensitivity and specificity, but ultimately intraoperative decisions are made based on clinical judgment.52,56,57,58

There do exist defined contraindications to marginal mandibulectomy, and these include gross destruction of the cancellous portion of the mandible demonstrated on preoperative radiographic studies, invasion of the mandibular canal by cancer, massive soft tissue disease surrounding either the lingual or lateral cortex of the mandible, and presence of tumor on the alveolus of an irradiated edentulous mandible.59 Irradiated mandibles typically demonstrate an infiltrative pattern of bone involvement, often at multiple points along the cortex, and many consider any history of radiation to be a contraindication for a marginal mandibulectomy.59

For surgical treatment of mandibular alveolus and RMT carcinomas, marginal mandibular resection has the advantage of maintaining the continuity of the mandible, although it theoretically involves a compromise between complete eradication of the tumor and conservation of the form and function of the mandible. Under select circumstances, guided by preoperative examination and radiographic studies, in addition to intraoperative assessment, marginal mandibulectomy is an oncologically sound surgical procedure.60

As mentioned earlier, the presence of pathologic cervical lymphadenopathy is a bad prognostic factor in both mandibular alveolus and RMT carcinomas. Histologically, lymph nodes are involved in 26 to 88% of these patients, with occult metastases
being present in 8 to 64% of patients after surgical treatment of the neck. Typically, neck metastases are ipsilateral, though contralateral nodal involvement has been reported. Because the frequency of occult metastases is not clearly established, in the absence of clinical or radiographic regional metastases, most authors recommend an ipsilateral supraomohyoid neck dissection (ND) for both staging and evaluation of microscopic metastatic disease.

### 9.6 Prognosis

With appropriate surgical management of the mandible and the neck, surgical resection with postoperative radiation +/- chemotherapy has become the most widely used treatment. Based on this paradigm, 5-year disease-free survival rates range from 49 to 69% for all RMT and mandibular alveolar lesions. Overall 5-year survival rates range from 26 to 61% for RMT lesions and 30 to 84% for mandibular alveolar lesions. With RMT lesions, there is no direct correlation between prognosis and clinical stage. However, extent of disease, whether it be bony involvement or masticator space involvement, has been shown to be an important determinant of outcome. Selected studies have shown decreased overall survival with positive margins and positive regional lymph nodes. Similarly, surgical margin status has been shown to be a significant prognostic factor in mandibular alveolar carcinoma.

### 9.7 Conclusion

The RMT and the mandibular alveolus are two unique anatomical subsites, characterized by their close proximity to the mandibular cortical bone. Preoperative assessment of bony involvement can be difficult, and often clinical examination is used in conjunction with multiple imaging modalities in order to estimate the extent of mandibular invasion. While the rarity and aggressiveness of these tumors have made randomized prospective analyses difficult, the mainstay of treatment has become surgical resection and reconstruction followed by radiation therapy. The goal of upfront surgery is to achieve negative margins, with many performing elective ipsilateral nodal dissection due to the high rates of locoregional recurrence. Both marginal and segmental mandibulectomy have an appropriate role in the management of this disease, and the extent of bony resection is often dictated by an integration of the preoperative clinical and radiographic workup with the intraoperative assessment of the bone. While further studies are needed to investigate the accuracy of various imaging modalities to predict the extent of bony involvement, thus determining the
References


Carcinoma Involving the Mandibular Alveolus and Retromolar Trigone
Reconstruction of the Mandible and Composite Defect

10 Reconstruction of the Mandible and Composite Defect

Shawn Li and Rod P. Rezaee

10.1 Introduction

The mandible is a prominent anatomical structure in the craniofacial skeleton. It is the only movable facial bone, and has both functional and aesthetic importance. The mandible is involved in articulation, mastication, and facial definition. It also serves to protect the delicate craniofacial structures from blunt force trauma. The classic American masculine feature is defined by a square, chiseled jaw, and elite boxers who have never been knocked out are deemed to have a “good chin.” Although the mandible does not have a significant role in preventing concussions as compared to the cervical/spinal musculature, these examples nevertheless serve as accepted recognition that the jaw is one of the defining features of the face.

The mandible therefore has great importance and warrants special consideration during reconstruction of head and neck defects. Segments of bone must sometimes be removed due to tumor growth, necrosis, infection, or instability. Depending on the extent of the resection, complex reconstruction is often necessary. This can be a challenging task as it involves a thorough grasp of three-dimensional (3D) structural relationships, consideration of associated soft tissue defects, and careful planning to recreate the appropriate contours. Eventual function must also be regarded—from jaw mobility for effective mastication to the restoration of the alveolar sulcus to minimize tongue tethering and improve food transit.

The introduction of the metallic reconstruction plate in the 1980s dramatically improved stabilization of mandible fractures. Anatomical reduction of fractured segments allowed for higher rates of union and return to baseline function. The same concept can be applied to segmental defects. The gap can be bridged by replacement of osseous tissue and stabilized with durable hardware. In recent years, free osseous tissue transfer has emerged as the gold standard in mandibular reconstruction and is often the first choice. However, alternatives do exist, and it is important to have a thorough grasp of the various options and their indications for use.

This chapter provides a brief overview of mandibular anatomy, classifies the common defects encountered, and describes the various reconstructive options. The objective is to provide the reader with a reasonably broad understanding of the reconstructive ladder when applied to mandibular and its associated soft tissue (composite) defects. Detailed ablative and donor-site harvesting techniques are beyond the scope of this chapter, although key tips and pearls are included. Additionally, there is a discussion on the latest advancements and possible future directions for research.

10.2 Anatomy of the Mandible

The mandible is embryologically derived from mesodermal elements. In fetal development, there are two distinct methods of ossification: intramembranous and endochondral. In short, the endochondral process requires initial hyaline cartilage formation, while the intramembranous process does not. The mandible forms mostly by intramembranous ossification. While Meckel's cartilage serves as a template for its formation, it is actually only an outer fibrous membrane which becomes ossified. The rest of Meckel's cartilage regresses except for a superior portion that forms the incus and malleus as well as the anterior ligament of the malleus and the sphenomandibular ligament. The jaw begins as two J-shaped hemimandibles, which then fuse at the midline to finalize into a U-shaped configuration. Since Meckel's cartilage is derived from the first pharyngeal arch, there is a close association of the mandible with the trigeminal nerve and the muscles of mastication. The primary ossification center on each side is located at the branching of the mental nerve from its inferior alveolar roots. As ossification proceeds medially and laterally, the nerve becomes housed within this canal.

In contrast, the condyle is formed via endochondral ossification. Condylar cartilage occupies most of the developing ramus and gives rise to the condyle head and neck of the mandible. The condylar head is intimately involved with the temporomandibular joint (TMJ). This is a complex bi-arthroidal hinge joint that allows for both translational and rotatory motion. Various important structures within the glenoid fossa as well as the surrounding ligamentous attachments help support the joint to maintain stability with repeated trauma from mastication and articularation. Because of the complexity of this region, reconstruction in this area can be difficult and often suboptimal. Various autologous and prosthetic grafts have been tested to simulate normal joint anatomy.

The mandible is separated into discrete segments. Classically, it is divided into the coronoid, condyle, ramus, angle, body, and symphysis. Each segment has unique anatomical considerations that may be important when planning for reconstruction. Some defects may span multiple segments. A brief description is provided for segments with key functional and cosmetic considerations.

10.2.1 Condyle

The condyle is unique because of its intricate association with the glenoid fossa. It is suspended from the skull base via multiple ligamentous attachments and has a rounded capsule at the head that connects the mandible with the articular disc. It is this articulation that allows for both rotational and translational movement when the jaw is opened maximally. Failure to reconstruct the condyle can result in postoperative shifting of the mandible and malocclusion.

Note

Failure to reconstruct the condyle can result in lateral shifting of the mandible and malocclusion. This can be both functionally debilitating and painful.

Various autologous and allograft materials have been used in TMJ reconstruction. This ranges from Silastic and Teflon to fascia and cartilage grafts. Gordon was the first to describe the use of an allograft prosthesis in condylar replacement in 1955.
Since then, various metallic implants have been tested; the two most well-known are the Christensen implant and the titanium-coated hollow-screw reconstruction plate (THORP) with a condylar head attachment. Metal prostheses, however, are fraught with complications (▶ Fig. 10.1a, b). They have been shown to cause glenoid fossa resorption in up to 43% of cases, leading to heterotopic bony formation (52%) and fixation of the joint. Excessive wear and tear also leads to skull base erosion with displacement of the implant into the middle cranial fossa, leading to hearing loss, facial nerve paralysis, and other neurologic sequelae. Hardware extrusion and failure also occur, especially in the setting of adjuvant radiation. As a result, some studies have shown up to a 30% removal rate for condylar prostheses.\(^5\)

**Note**

Metal prostheses are fraught with complications including resorption of the glenoid fossa, fixation of the joint, and skull base erosion with displacement of the implant into the middle cranial fossa.

Autologous rib grafts have also been used. Any free grafts, however, are susceptible to unpredictable resorption and infection. In addition, some studies have reported overgrowth of the costochondral graft when used for TMJ reconstruction.\(^6\) Therefore, while free grafts may be considered for the short condylar reconstruction, larger segmental defects involving the entire lateral mandible necessitates vascularized bone flaps (▶ Fig. 10.2).

While it is possible to attach a prosthesis, rib graft, or the detached native condyle to the distal end of a vascularized bone graft, the same complications described above can occur. At our institution, we find that the distal end of osteocutaneous flaps can be molded to fit snugly into the glenoid fossa directly (▶ Fig. 10.3). This can then be secured by nonabsorbable sutures or with the creation of muscular sling through the attachment of the masseter to the pterygoid (▶ Fig. 10.4).

### 10.2.2 Ramus

The ramus is a straight segment of bone that in itself may not be challenging to reconstruct. However, defects involving the ramus are often accompanied by significant soft tissue loss and potential involvement of the condyle. Both of these can dictate...
a higher level of complexity. Often, the coronoid is resected to reduce postoperative trismus from contracture and scarring of the temporalis attachments.

### 10.2.3 Body

This is the least complex area to reconstruct as it is essentially a straight segment of bone. The mylohyoid line runs obliquely along the body and muscular attachments here form a barrier between the oral cavity and the neck. However, it is usually not necessary to resuspend glossal attachments here. One special consideration is that the bone must be angled lingually to allow for optimal positioning of dental implants.

**Note**

Although the mandibular body is the least complex area to reconstruct because it requires a straight segment of bone, one special consideration is that the bone must be canted slightly lingual to allow for optimal positioning of dental implants.

### 10.2.4 Symphysis

The symphysis is a difficult segment to reconstruct due to its importance in facial projection. The mandible takes a sharp curve in this area, and appropriate contouring requires careful planning and multiple osteotomies when using osteocutaneous free flaps (▶ Fig. 10.5, ▶ Fig. 10.6, ▶ Fig. 10.7). The genioglossus and suprhyoid musculature also attach here and must be reattached to maintain proper anterior tongue and hyoid position. Failure to resuspend suprhyoid musculature can result in impairment in swallowing as well as sagging of the anterior neck line (▶ Fig. 10.8).

Defects here also usually involve associated anterior floor of mouth tissue loss. Osteocutaneous free flaps with thinner, pliable soft tissue components are ideal to recreate the natural alveolar ridges to prevent tongue tie and to allow for fitting of dentures.

**Note**

When reconstructing the mandibular symphysis, it is important to resuspend suprhyoid musculature. Failure to perform the resuspension can result in glossoptosis, impairment in swallowing, and aspiration.

### 10.3 Goals for Reconstruction

For smaller defects excluding the condyle, the ideal reconstruction simply involves bridging the anatomical bone gap. With appropriate bony union and restoration of contour, there is reduced risk of fractures and instability over time. For larger defects and those involving the condyle, function becomes a concern. Recreation of the TMJ is often not possible, but close reapproximation will allow adequate function if the contralateral joint remains undisturbed. The same applies for loss of masticator and glossal muscle attachments.

Reestablishing baseline occlusion is a key element in the restoration of form and function. This can be more easily
achieved with intermaxillary fixation followed by temporary fixation of the titanium bar prior to resection. This allows for preresection contouring and optimal templating prior to extirpation of the tumor. In cases where there is significant deformity of the buccal cortex or symphysis, this technique may not be possible. Post-reconstruction occlusion must be carefully assessed and necessarily adjustments can then be made. Virtual planning and the use of prefabricated hardware can also be of value. This is described later in the chapter.

Finally, appearance is an important concern. The mentum, gonion, and pogonion are vital landmarks in facial analysis, and recreation of anatomically acceptable angles is key when considering psychosocial well-being.

### 10.4 Evaluation of the Defect

Intuitively, the type of defect dictates the optimal options for reconstruction. There are a variety of classifications proposed in the literature to categorize mandibular defects. Beginning with Pavlov in 1974, a three-tier classification system was created that solely addressed bony deficiencies. More recently, classification systems have realized the importance of the concomitant mucosal and/or skin defects in reconstructive planning and have incorporated this into their respective schemes.

One such system was proposed by the Mount Sinai Group in 1991. This proposed anatomical classification system was complex, offering more than 3,500 possible oromandibular defects. Although thorough, this system was complicated, thus limiting its practical use in designing a reconstructive algorithm. The University of Toronto group led by Boyd subsequently proposed a simpler classification system using uppercase letters to denote the bony defect and lowercase letters to convey the involvement of skin mucosa, skin, and the combination of skin and mucosa. C, L, and H are used to designate anterior defects spanning canine to canine and lateral defects with and without condylar involvement, respectively. The letters o, s, m, and sm refer to no epithelial component, skin, mucosal, or both.
Unfortunately, none of the published classification systems are widely used. Although a classification system has the potential to provide a framework for reconstructive algorithms, it has proven difficult to incorporate the functional and aesthetic complexity of mandibular defects into a simple classification system. Instead, each case requires the surgeon to carefully analyze the defect and determine the reconstructive option that best suits the complexity of the tissue loss. Three key factors are considered: length of defect, size of epithelial defect, and whether both skin and mucosal defects are present. ▶ Fig. 10.9 shows a simplified algorithm based on these factors. This algorithm can be applied to a majority of extirpative results. Rarely, more complex encounters will likely necessitate some creative thinking and/or the combined use of multiple graft options.

### 10.5 Options for Reconstruction

There are a variety of ways to reconstruct a mandible defect. This ranges from as simple as a bridging titanium bar to as complex as a composite free vascularized graft. Each has its advantages and disadvantages, and often other factors such as patient comorbidities are taken into consideration. In general, a vascularized bone graft achieves superior results when compared to free bone graft or no bone graft. At high-volume centers, the efficiency of free flap transfer is optimized such that often there is no significant increase in operative time and patient morbidity. While understanding the indications for nonvascularized graft is important, its use has become less common.

Each free flap option has its own unique advantages and disadvantages (▶ Table 10.1). However, surgeon experience and preference is also an important consideration. Ultimately, any of the following options can be used in the majority of cases. Most centers use the fibula free flap as the workhorse flap for mandibular reconstruction. It is versatile, easy to harvest, and has consistent anatomy. Oftentimes, other options are only considered if there is a contraindication such as severe atherosclerosis, aberrant lower leg vasculature, previous significant orthopaedic procedures, or if both fibulas have already been harvested. Sometimes, significant soft tissue requirements make scapula a better option but cuffs of soleus and flexor hallucis muscle can also be harvested with the fibula to help fill defects and provide additional soft tissue.

**Note**

While the fibula free flap is considered the workhorse flap for mandibular reconstruction, however, in cases of severe atherosclerosis, aberrant lower leg vasculature, or a significant soft tissue requirement, the scapula may make a better option.

However, some surgeons have extensive experience with other osteocutaneous flaps such as the radial forearm and scapula. They are then able to push the envelope with these flaps and...
can achieve similar efficiency and results. Iliac crest has fallen out of favor in recent times. It has remained in use by oral maxillofacial microsurgeons in some centers. Selection of donor site then depends on a combination of patient and surgeon factors. It is up to the surgeon to be familiar with all the options and find one in which he or she is most comfortable with to maximize patient outcomes.

### 10.5.1 Nonosseus Options

A bridging titanium bar is the simplest option to restore contour and maintain stability. Historically, this has been fraught with complications with high incidences of failure. Scar contracture can lead to eventual plate erosion either intraorally or externally. Even the largest reconstruction bars cannot withstand the forces of mastication over time, as the bridging segments have empty holes with small cross-sectional volumes. Eventually, without bony regeneration, all plates have an increased risk of breakage especially in the dentate patient. Screws can also loosen over time, leading to instability of fixation. Without new bone to bridge the defect, hardware failure results in swinging mobile mandibular segments.\(^\text{12}\)

Consequentially, there is still a small role for the use a bridging titanium plate, albeit only with soft tissue coverage and for lateral defects. Anterior defects must be reconstructed with bone as the rate of plate failure with anterior forces is unacceptably high. Therefore, nonbony reconstruction is usually reserved for the patient who has more medical comorbidities, and may be at increased risk for complications with lengthier procedures. In bony defects without a significant soft tissue, mucosal or skin component, the fibula can be harvested in a similar time frame as a radial forearm or anterolateral thigh (ALT) flap. There would then be no benefit to avoiding a bony flap. However, as discussed later in this chapter, the fibula and iliac crest in general have more limited design flexibility for skin paddles. In defects requiring more complex soft tissue or mucosal coverage, a scapula or latissimus may increase surgical time as, although possible, it is generally more of a challenge to harvest simultaneously. In these cases, either a regional (pectoralis) or free flap used with a bridging plate can significantly reduce operative times.

#### Table 10.1 Anatomical properties of osteocutaneous free flaps

<table>
<thead>
<tr>
<th>Donor site</th>
<th>Length (cm)</th>
<th>Height (mm)</th>
<th>Cortical thickness (mm)</th>
<th>Pedicle length</th>
<th>Skin and soft tissue</th>
<th>Preoperative testing</th>
<th>2-team harvest</th>
<th>Donor-site morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibula</td>
<td>25</td>
<td>17</td>
<td>3–4 (bil)</td>
<td>Long</td>
<td>Medium</td>
<td>Angiogram</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Radial forearm</td>
<td>12</td>
<td>15</td>
<td>2–30 (mono)</td>
<td>Long</td>
<td>Medium</td>
<td>Allen’s test</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Scapula</td>
<td>14</td>
<td>30</td>
<td>3–4 (mono)</td>
<td>Medium</td>
<td>Large</td>
<td>None</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Femur</td>
<td>10</td>
<td>15</td>
<td>6–7 (mono)</td>
<td>Medium</td>
<td>Large</td>
<td>None</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Serratus</td>
<td>15</td>
<td>15</td>
<td>1.5–2 (bil)</td>
<td>Long</td>
<td>Small</td>
<td>None</td>
<td>No</td>
<td>Medium</td>
</tr>
<tr>
<td>Iliac crest</td>
<td>15</td>
<td>40</td>
<td>2–3 (bil)</td>
<td>Short</td>
<td>Medium</td>
<td>None</td>
<td>Yes</td>
<td>High</td>
</tr>
</tbody>
</table>

**Note**

A reconstruction bar without bone restoration cannot withstand the forces of mastication. Over time, plates have an increased risk of breakage and extrusion. This is particularly true in patients previously treated with radiotherapy.

### 10.5.2 Free Bone Graft

Starting just after World War II, mandibular reconstruction began with the use of free grafts. The advent of metallic hardware allowed for a semistable housing unit to contain these grafts to maximize chance of take. Initial failure rate was high, largely attributed to infection, but with advances in antibiotics, this improved. However, large nonvascularized bone grafts still had significant rates of resorption, and are not first line for reconstruction of defects greater than 5 cm.\(^\text{14}\)

### 10.5.3 Physiology of Bone Grafting

Bone grafting is a simple formula that requires two key ingredients: free bone cells, and a vascularized bed for integration. The initial graft forms the primitive osteoid matrix, then new
Reconstruction of the Mandible and Composite Defect

Bone formation occurs via two mechanisms: osteoconduction and osteoinduction. Osteoconduction involves the resorption of grafted cells by osteoclasts with simultaneous deposition of new bone by native osteoblasts. This means a certain percentage of the initial volume of transplanted cells is always resorbed and, therefore, the initial density of grafted cells is important. Since cancellous bone can be packed more tightly, it has greater osteogenic potential than cortical bone and is often the preferred tissue harvested for grafting.

Osteoinduction implies that pluripotent cells in the tissue bed are stimulated to differentiate into osteoblasts, which leads to new bone deposition. Finally, remodeling occurs in response to mechanical stress.

When considering a free bone graft, two techniques are available for reconstruction. The first is to obtain an entire corticocancellous segment of bone to bridge the continuity defect and stabilize with a rigid titanium plate. This is usually harvested from the anterior and posterior ilium as there is abundant bone to buffer the inevitable partial resorption. The second option is to utilize a mesh tray around the defect and fill it with packed cancellous bone. Again, the posterior ilium is a good option here, along with tibia, rib, and calvarium as potential options.

10.5.4 Nonautologous

Bone morphogenetic protein 2 (BMP-2) is a recombinant protein that has potential for osteoinduction. It has been shown to induce osteoblast differentiation and is integral to bone production. In the extremities, BMP-2 has been successfully used as stand-alone grafting material as well as adjunctively with autologous bone grafts. A few papers have also cited the successful use of BMP-2 in various mandibular defects. This is often placed within a collagen carrier and housed in a titanium tray. At 3 to 4 months, new bone was palpable, and at 5 to 6 months, radiographic evidence of neo-ossification was present. Further research needs to be done, but this shows the potential of allograft material in mandibular reconstruction. The advantages are obviously decreased donor-site morbidity and the ability to generate an unlimited abundance of grafting material. Whether this can be more successful than free bone grafting remains to be seen and its use in cancer patients may be limited.

10.6 Composite

10.6.1 Local Regional

The first attempts at vascularized bone grafts used locally available sources. Reports of pectoralis myocutaneous flaps with rib and sternocleidomastoid muscle flaps with clavicle are available. While initially promising, long-term results were much less favorable. Donor-site morbidity as well as limited reconstructive freedom made these poor candidates. The blood supply was also less robust, leading to higher rates of failure and resorption. The volume of bone available for transfer was also suboptimal.

10.6.2 Fibula

The fibula has become the most commonly used osteocutaneous free flap in mandibular reconstruction. It is incredibly versatile and has many advantages. The anatomy is reliable, the pedicle is long, and the graft can be harvested in a two-team fashion. The fibula also provides the longest segment of bone and is capable of restoring near-total mandibular defects. A thin skin paddle can also be raised with it to cover mucosal and skin defects. In addition, while the fibula is only half the thickness of a dentate mandible, it does have sufficient cortical bone to allow for eventual placement and integration of dental implants.

Preoperative testing is important when considering the fibula for free tissue transfer. The lower leg typically has a three-vessel runoff, making the peroneal (or fibular) artery redundant as a blood supply for the plantar arch. However, 3.8% of patients can have hypoplastic or absent posterior tibial arteries, making the peroneal artery the major contributor to the plantar arteries.

Harvesting of this vessel would then place the foot at high risk for ischemia. In addition, 1.6% of patients do not have anterior tibial vessels. The dorsalis pedis arteries in these cases are dependent on the anterior perforating branch of the peroneal artery. Finally, significant atherosclerotic disease can pose similar scenarios for harvesting of the peroneal artery. Plaque burden can also directly affect the peroneal artery, significantly increasing the risk of vessel thrombosis and flap failure.

Various studies are available to assess lower extremity vasculature. This ranges from noninvasive options such as palpation, ankle-brachial indices (ABI), and duplex studies to more complex CT/MRI studies and formal angiography. At our institution, we prefer CT angiography (CTA) as a preoperative tool with magnetic resonance angiography (MRA) as an alternative for patients with significant kidney disease. We have found that the color flow Doppler is less likely to detect anatomical abnormalities when compared to angiogram, CTA, or MRA. Garvey et al have also shown the CTA to be useful in assessing perforator anatomy. Perforator location was within 8.7 mm of CTA predictions and 25% of the cases required modifications in skin paddle and osteotomy design based on CTA findings.

Up to 25 cm of bone length can be harvested. Donor morbidity is minimal as the fibula is a non-weight-bearing bone. However, at least 5 cm of bone must be preserved superiorly to protect the common peroneal nerve, and a similar segment preserved inferiorly to prevent instability of the ankle joint. Oftentimes, full segments of fibula are harvested regardless of the defect. The pedicle can then be freed from its proximal bony attachments and appropriate bone shortening performed. This allows for the longest possible vascular pedicle, allowing microvascular anastomosis in a vessel depleted neck to the contralateral side or the low transverse cervical or thoracoacromial vessels if needed.

A long pedicle also allows for freedom in flap geometry. Since the peroneal vessels run on the medial surface of the bone, this is often the side that must face medially when reconstructing the mandible in order to reduce incidence of injury from
drilling and plating. Thus, the orientation of the pedicle largely depends on site of defect and site of harvest. For example, reconstruction of a right-sided mandibular defect using the right fibula will result in the pedicle being oriented posteriorly. This may be problematic if the anastomosis has to reach the contralateral or lower neck. Instead, harvesting the left fibula will result in a pedicle that is oriented anteriorly. Although either leg can be used, the reconstruction must consider these concepts when preparing the patient especially as it pertains to skin paddle placement for soft tissue replacement.

**Note**
The position of the skin paddle (intraoral vs. extraoral) and the orientation of the vascular pedicle (posterior vs. anterior) will dictate the side of the harvest.

When the fibular flap was first used, there were concerns regarding the reliability of the skin perforators and the size of skin paddles that could be harvested. Minor adjustments such as the inclusion of the posterior intermuscular septum and designing of the skin paddle to lie over the middle to distal third of the fibula has reduced the failure of skin paddles. In addition, large flaps up to 10 cm × 20 cm in size can be harvested if multiple perforators are identified and preserved. Although primary closure is possible in some cases, closure usually requires a split-thickness skin graft as there is significant tension generated in this area due to contraction of plantar flexor muscles. Dehiscence can lead to troublesome chronic wounds and exposed tendons.

**10.6.3 Iliac Crest**
The iliac crest is a source of extensive bone and has been used frequently in the past for reconstruction of mandibular defects. This flap can be harvested with the deep circumflex iliac pedicle and used in free microvascular transfer. However, the pedicle is limited in size and length, making design variations difficult. Skin and internal oblique muscle can also be harvested but is again limited by decreased arc of rotation. While the bone stock here is the highest in caliber, there is potential for significant donor-site morbidity. High incidence of postoperative pain, hernia, neuropathy, and impotence can be debilitating. This has limited the popularity of the iliac crest in favor of other options.

**10.6.4 Scapula**
The scapula free flap was first described by Saijo in 1978. It is perhaps the most versatile free flap, providing excellent bone stock in addition to extensive soft tissue and skin possibilities. The subscapular vasculature is not prone to atherosclerotic changes and no preoperative testing is required. The only relative contraindication is previous axillary lymph node dissection, and the main limitation is the inability for a two-team approach.

The circumflex scapular artery provides the main supply to the lateral aspect of the scapular bone. However, the angular branch of the thoracodorsal artery can be dissected to include the scapular tip as a separate graft or in continuity with the lateral scapula for a bony segment up to 14 cm in total length. Many variations have been described that include nearby tissue such as the latissimus dorsi, serratus anterior, scapular, and parascapular skin. This allows for significant flexibility in 3D designing and can be tailored to reconstruct virtually any defect.

**Note**
The scapular flap is perhaps the most versatile free flap, providing excellent bone stock in addition to extensive soft tissue and skin possibilities. This donor site is ideal for complex 3D defects.

**10.6.5 Osteocutaneous Radial Forearm**
The radial forearm is arguably the most popular fasciocutaneous free flap in head and neck reconstruction. It is easy to harvest, has a reliable and lengthy pedicle, and provides large islands of thin pliable tissue that is ideal for recreation of complex mucosal defects. Preoperative screening with an Allen’s test is necessary to confirm adequate ulnar supply to the palmar arch before the radial artery can be harvested. While the sensitivity of an Allen’s test is as high as 100%, Doppler ultrasonography can be used to increase the specificity for suboptimal anatomy when there are equivocal physical examination findings.

Dissection of the deep periosteal perforators of the radial artery allows for inclusion of a monocortical segment of radius bone. Grafts up to 10 cm can be taken but only 50% of the radius thickness can be harvested. Prophylactic internal fixation of the remaining radius using bicortical screws proximal and distal to the defect significantly reduces the incidence of postoperative fracture. This has been extensively used and studied by the University of Kansas Head and Neck team.

The main advantage of the osteocutaneous forearm flap is its versatile, abundant skin paddle. Often times, the complexity of the mucosal defect dictates the optimal reconstructive option. The thin, pliable tissue of the forearm allows for ideal recreation of the oral mucosa. The moderate vascularized bone stock of the radius allows for simultaneous bridging of smaller segmental defects.

**Note**
The main advantage of the osteocutaneous forearm flap is its versatile, abundant skin paddle.

**10.6.6 Serratus**
The serratus flap with anterior rib is a good alternative for bone-only defects, often due to benign tumors or radionecrosis. It is based off the thoracodorsal pedicle which has reliable anatomy and is rarely affected by atherosclerosis. It has a long pedicle and the blood supply to the anterior rib through the lower serratus interdigitations is robust compared to the tentative fascial connections provided through the pectoralis
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and latissimus flaps. The cortical bone is thinner here compared to iliac crest or fibula, and may not be suitable for dental implantation. However, the length of bone available is often greater than scapula and is much easier to contour. In addition, multiple rib segments can be taken as long as an intervening segment is left in place to prevent flail chest. The serratus can be harvested with scapula and latissimus tissue for a chimeric flap if extensive soft tissue coverage is needed. Positioning can often be a challenge and may preclude a two-team approach. A lateral approach is possible through a midaxillary incision that may facilitate simultaneous harvest and resection; however, this can be limited by body habitus.

10.6.7 Femur

The medial femoral condyle flap was originally described by Lapierre in 1991 as a corticoperiosteal graft used to cover skull defects.22 It was then adapted to treat problematic nonunion in the upper and lower extremities. The pedicle is relatively short (up to 7 cm) and smaller in caliber when compared to the popular fibular vessels. It is based off the descending genicular artery, which is a medial branch of the superficial femoral system. In recent years, the use has expanded as entire corticocancellous segments up to 10 cm in length have been harvested to reconstruct maxillary and mandibular defects.23

The main advantage of this flap is the thickness of its cortical bone and durability for placement of dental implants. As a thin monocortical segment, it may be less robust for bridging anterior segmental defects, but can be adequate for lateral defects involving the ramus and condyle. The blood supply is also more tenuous and may not allow for osteotomies. It has been recently described as an ideal option for reconstruction of the alveolar ridge. Donor-site morbidity is minimal if less than 1.5 cm of thickness is taken. However, surgeons will still advocate for 6 weeks of limited weight bearing on the donor leg. Although this is an intriguing and novel technique in the armament of head and neck reconstruction, further research is needed to establish its full potential.

Note

The main advantage of the vascularized femur flap is the thickness of its cortical bone and durability for placement of dental implants.

10.7 Three-Dimensional Modeling and Virtual Planning

Recent advances in virtual surgical tools have intriguing implications for mandibular reconstruction (Fig. 10.10). Recreating the complex 3D shape of large mandibular segments with a straight fibula can be challenging. This often requires time bending reconstruction bars and performing multiple osteotomies, adding to ischemia and total surgical time. The process can be unforgiving, with small mistakes in osteotomy design significantly impacting final results.

Technological advances have emerged providing presurgical options whose aim is to potentially improve the accuracy of the mandibular contour and expedite the process of bending the plate intraoperatively (Fig. 10.11). The process involves using preoperative thin-cut craniofacial and lower extremity CT scans to create a 3D virtual model of the resection site. Then, the surgeon can virtually plan the resection with computer models and simulate the necessary osteotomies for optimal configuration of the graft. A customized prebent plate and osteotomy guides can also be manufactured for intraoperative use. Turnaround time for this process can be 7 to 14 days and must be considered and not delay patient care. Options exist for expedited manufacturing when needed and with proper communication with the manufacturer.

There are several advantages with this paradigm. First, careful computer-aided planning can result in more optimal orthognathic occlusion, especially when considering defects that span the anterior mandible. Chin projection can be carefully adjusted ahead of time rather than in the intraoperative setting of a long procedure. Secondly, prebent hardware and osteotomy guides give the potential to reduce operative time and excess handling of delicate graft tissue as adjustments are made with traditional intraoperative modifications. In addition, well-designed resection guides and osteotomies results in optimal bone-to-bone contact. This can improve union and overall stability of the neomandible.

Note

Computer-aided planning can result in more optimal orthognathic occlusion, especially when considering defects that span the anterior mandible. This advantage comes at a financial cost that must be considered.

Disadvantages include increased cost and, occasionally, changes in surgical planning based on tumor growth. Virtual planning
adds cost to the procedure, although this likely will decrease with time and more widespread use. However, in the appropriate cases, reduction in operative time and improvements in outcome may offset this cost. Some variation in actual surgical encounters can be buffered by the creation of additional osteotomy guides proximal and distal to the expected segmental defect.24

10.8 Dental Implants

Ultimately, full restoration of function in mandibular reconstruction involves dentate mastication. This can be done either through the use of simple dentures or with more permanent prosthetic bridges and dental implants. A simple prosthesis relies on existing teeth for stability and is inadequate if the patient is edentulous. Therefore, titanium osseous implants have emerged as the gold standard in restoration of oral function.

There are many challenges in recreating dentition in a reconstructed mandible. First, grafted segments are usually less than half the thickness of the native toothed mandible, especially in the anterior segments. Since the graft is often aligned with the inferior border, this leaves a significant gap in contour at the alveolar ridge. Second, there are often associated soft tissue and mucosal defects which undoubtedly distorts the normal mucosal sulci. Most initial mucosal reconstructions will end up with tethering and flattened a contour due to the thickness of grafted tissue compared to the thin native mucosa. Both of these factors preclude the use of dentures and can limit the success rate of implants unless revisions are performed first.

Some techniques have evolved to increase the success rates of dental implants. First, the implants can be placed bicortically to increase stability. The fibula bone is ideal for this as it has a thicker bony cortex when compared to the iliac crest or scapula. In addition, some surgeons have advocated for the double-barreled fibula technique, utilizing a separate segment of bone to recreate the superior contour of the mandible. This better reapproximates native mandible height and also allows for the placement of tricortical implants that extend through both graft segments. The same principle can also be applied to the osteocutaneous radial forearm flap. Second, careful planning is required to minimize placement of implants in compromising locations. Osteotomy sites and areas with existing monocortical screws from plate fixation are not appropriate areas for implantation. Additionally, recreation of the gingival sulcus through delayed flap thinning and vestibuloplasty can help create space for the prosthesis.

Techniques have evolved to increase the success rates of dental implants that include bicortically implant placement, double-barreled fibular bone grafts, and careful placement of the implants to optimize placement into well-vascularized bone segments.

Implants can be placed immediately at the time of reconstruction, or in a delayed fashion. We do not routinely perform...
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immediate dental implantation. The limited benefit and patient convenience associated with this do not outweigh the added challenges involved in preoperative planning, increase in operative time, and potential for complications and/or treatment failures. Financial limitation is also an important factor as implants are a costly endeavor and often not a covered medical benefit.

While success rates for titanium osseous integration are high, 92% are without radiation and even 86% with radiation. The ultimate success of dental rehabilitation can still be significantly lower, at less than 50%.24 This is because recreation of useful prosthesis involves additional complexities such as proper occlusion, oral hygiene, and mucosal tissue health. Improper angulation of implants either due to initial design flaws or changes from the healing cycle can severely limit proper prosthetic placement. Recent advances in virtual planning can also play an important role in dental rehabilitation. The ability to create prefabricated drilling templates based on virtual osteotomy designs can dramatically improve the success rate and functionality of implants and prosthesis.

10.9 Conclusion

Mandibular reconstruction is a complex task for the head and neck surgeon due to the wide variety of defects that can be present. With each case, there are unique challenges in restoring form and function. Many goals have to be addressed including adequate epithelial coverage, maintenance of functional occlusion, restoration of bony union, and recreation of appropriate aesthetic contour. Fortunately, a plethora of options are available, ranging from no bone replacement to free bone grafts to vascularized osteocutaneous free flaps. While the fibula has emerged as the most popular donor site, other flaps such as the radial forearm, scapula, medial femoral condyle, serratus, and iliac have their own unique advantages. Furthermore, technologies such as virtual planning and tissue engineering are on the horizon, and have significant potential for future advancement.

References

11 Open Management of Carcinoma of the Oropharynx

Robert H. Lindau, Andrew M. Coughlin, Erin R. S. Hamersley, and Dana K. Petersen

11.1 Introduction

Medicine has seen many evolutions and changes over the last thousand years. Technology has at times driven treatment modifications; however, better understanding of the disease process is oftentimes the catalyst. As we look back on this current era in medical history, we will likely see how both knowledge of a disease process and the technological development have evolved our understanding and transformed our care of patients with oropharyngeal cancer.

11.2 Anatomy of the Oropharynx

The oropharynx is a muscular tube that extends from the skull base to the inferior border of the cricoid cartilage. It is divided into three distinct anatomical subsites from superior to inferior: the nasopharynx, oropharynx, and hypopharynx (Fig. 11.1). The oropharynx extends from the inferior surface of the soft palate when it is elevated. Anteriorly, it is separated from the oral cavity circumferentially by the junction of the hard and soft palate when it is elevated. Anteriorly, it is separated from the oral cavity circumferentially by the junction of the hard and soft palate when it is elevated.

The soft palate extends posteriorly and inferiorly from the hard palate and is composed of the palatoglossus, palatopharyngeus, levator veli palatini, tensor veli palatini, and musculus uvulae. It contains minor salivary glands and is mucosally covered. The soft palate elevates to achieve velopharyngeal closure during deglutition and speech. Motor innervation is supplied by the vagus nerve via the pharyngeal plexus for all muscles of the soft palate with the exception of tensor veli palatini, which receives its innervation from the trigeminal nerve.

The base of the tongue refers to the posterior third of the tongue between the circumvallate papillae and the vallecula. It contains both extrinsic and intrinsic tongue musculature and is covered by nonkeratinized squamous epithelium. Minor salivary glands and the lingual tonsils are located in the submucosal layer of the base of tongue. Motor innervation is supplied through the hypoglossal nerve. Sensory innervation is provided through the glossophyaryngeal and vagus nerves.

The palate tonsils are composed of lymphoid tissue located between the anterior and posterior tonsillar pillars. The pillars are composed of the palatoglossal muscles anteriorly and the palatopharyngeal muscles posteriorly and often referred to as the palatoglossal and palatopharyngeal folds. Vascular supply for the palatine tonsil is provided from the external carotid system through branches off of the ascending pharyngeal, lingual, facial, and maxillary arteries all of which are important when considering vascular control intraoperatively.

A mucosal layer lining the lumen of the pharynx covers the posterior and lateral pharyngeal walls. Deep to the mucosa and submucosa is the pharyngobasilar fascial layer followed by the superior and middle constrictor muscles. The farthest layer from the lumen is the buccopharyngeal fascial layer and covers the external surface of the pharyngeal constrictors.

The oropharynx is bordered by the retropharyngeal space posteriorly and the parapharyngeal spaces laterally. The retropharyngeal space extends from the base of the skull to the superior mediastinum. It lies posterior to the buccopharyngeal fascia and anterior to the alar fascia. Its lateral extent is the carotid sheath bilaterally. The retropharyngeal space houses retropharyngeal lymph nodes that can be involved with oropharyngeal tumors. The parapharyngeal space is a potential space that is bounded superiorly by the skull base and extends inferiorly to the hyoid bone. Anteriorly, it is bounded by the pterygomandibular raphe, posteriorly by the prevertebral fascia, medially by the pharyngobasilar fascia (superiorly) and the superior constrictor, and laterally by the deep lobe of the parotid, mandible, and medial pterygoid muscles. The parapharyngeal space is divided into the prestyloid and poststyloid compartments.

Lymphatic drainage of the oropharynx is predominantly to levels II and III; however, lesions are also capable of draining to levels I, IV, and rarely V1 (Fig. 11.2a, b). Midline structures may drain bilaterally. Additionally, the oropharynx has lymphatic drainage to the retropharyngeal lymph nodes. The lymphatic drainage pattern of the oropharynx should be considered when evaluating patients with oropharyngeal tumors, as it will indicate possible sites of metastases.

![Fig. 11.1](image-url)
Head and Neck Cancer | 19.07.19 - 12:03

Note

The lymphatic drainage pattern of the oropharynx should be considered when evaluating patients with oropharyngeal tumors, as it will indicate possible sites of metastases.

11.3 Human Papillomavirus Negative and Oropharyngeal Carcinoma

11.3.1 Epidemiology

Cancers of the oropharynx have shown a dramatic increase in incidence from 2.8 to 3.6 per 100,000 from the years 1988–1990 to 2003–2004, respectively. Much of this increase is related to the human papillomavirus (HPV) epidemic, whereas the incidence of HPV-negative tumors has shown a decrease from 2 to 1 per 100,000.¹ HPV-negative tumors are similar to other subsites within the head and neck in that these have generally been related to heavy tobacco and alcohol use. These other upper aerodigestive tract tumor subsites have also been decreasing in incidence over the same time period.² Historical data representing more of this HPV-negative cohort suggest that males account for more oropharyngeal tumors than females (2:1). African American males, however, are twice as likely as white males to have oropharyngeal cancer and the male-to-female incidence rate is even more pronounced at 5.5:1.³ Minor salivary gland malignancies and sarcoma are some of the other more rare pathologies encountered in the oropharynx; however, squamous cell carcinoma (SCC) represents over 95% of these tumors and is the focus of this chapter.³

11.3.2 Etiology

In 1988, Blot et al presented their landmark paper proving that not only were tobacco and alcohol independently implicated in oral and pharyngeal cancers but that patients who smoked more than two packs per day and consumed more than four drinks per day had a synergistic effect leading to a 35-fold increased incidence in cancer above baseline.⁴,⁵ Other studies were performed and looked at patients with and without upper aerodigestive tract cancers and their tobacco abuse history. It was found that there was a 3.3% incidence rate of oropharyngeal carcinoma in 75-year-olds with continued smoking; however, this rate significantly dropped if patients stopped by age 50 (1.4%) or 30 (0.5%), or if the patient was never a smoker (0.2%). It is interesting that even patients who stop smoking by age 30 still had greater than 50% risk of developing an oropharyngeal malignancy compared to nonsmokers.⁶
Although we understand that alcohol and tobacco play a major role in the pathogenesis, it was Califano et al in 1996 who described the genetic model behind cancerization. They showed that as normal mucosa was continually exposed to carcinogens, multiple genetic alterations were made within tumor cells such as inactivation of tumor suppressor p16, mutations in p53 (present in 50% of head and neck cancers), and amplification of oncogenes such as cyclin D1. These alterations ultimately led to cell growth dysregulation and the progression of cells from normal mucosa, to dysplasia and finally invasive carcinoma.7 As the number of cigarettes used per day, the number of years the patient has smoked, and the intensity of alcohol drinking all increased, a significant increase in the odds ratio of developing non-HPV–related head and neck malignancies also occurred.8

Note
Genetic alterations develop in normal mucosa that is continually exposed to carcinogens such as inactivation of tumor suppressor p16, mutations in p53, and amplification of oncogenes such as cyclin D1. These alterations ultimately lead to cell growth dysregulation and invasive carcinoma.

11.3.3 Clinical Presentation
Patients presenting with oropharyngeal primary tumors often have symptoms of otalgia, dysphagia, odynophagia, voice changes, weight loss, and a slowly growing neck mass. Many of the things we do on a day-to-day basis such as swallowing, talking, breathing, and vocalizing all require involvement from the pharynx. Therefore, dysphagia and voice changes are very noticeable and bothersome to patients and primary lesions are typically diagnosed at an earlier stage unlike in hypopharyngeal tumors which typically present much later. Despite early T stage, many oropharyngeal cancer patients are usually diagnosed with advanced-stage cancers based on nodal metastases, as 65 to 93% of patients present with nodal disease at the time of diagnosis.9

With respect to patient characteristics non-HPV–mediated cancers tend to be found in patients who are older, nonwhite, single, not college educated, and have an annual income less than $50,000 per year.10

11.3.4 Work-up
Typically, patients presenting with a neck mass will undergo complete history and physical examination, including laryngoscopy to attempt visualization of the oropharynx and larynx. Especially in the case of an unknown primary, I prefer palpation of the oropharynx prior to fiberoptic laryngoscopy so that I can look for an area that bleeds in the case of a small primary tumor. If a suspicious lesion is appreciated, then complete examination of the upper aerodigestive tract with biopsy under general anesthesia is performed for definitive pathologic diagnosis as well as extent of tumor evaluation. Panendoscopy with esophagoscopy and bronchoscopy is also performed to evaluate for second primary malignancy, which can range in incidence from 9.4 to 14.2%11,12,13 with an annual incidence rate of 4 to 7%.14

A study by Khuri et al showed a second primary malignancy rate 7.4% in patients with pharyngeal cancers.15 More recent studies have shown a significant decline in oropharyngeal second primary malignancies; however, this is felt to be related to HPV-mediated tumors in never-smoking patients.16 Peck et al confirmed this trend, showing that the risk of second primary malignancy has decreased from 14.6 to 5.6% for HPV-positive oropharyngeal cancers. This study also showed that even in smokers, those with HPV positivity had better outcomes compared to their HPV-negative counterparts.17

Panendoscopy for patients with oral cavity and oropharyngeal carcinomas yield no second primaries in nonsmokers; however, 12% of patients had a second primary if they were smokers.18 Therefore, in our non-HPV–mediated cohort, panendoscopy should be strongly considered as part of the workup. Occasionally, patients will present with a neck mass and no specific mucosal findings. This clinical presentation is particularly more challenging to manage. Fine-needle aspiration (FNA) of the neck mass is typically performed first to obtain a tissue diagnosis as was first described by Hayes Martin in 1930,19 and a search for the primary lesion follows.

All patients must undergo imaging including either a computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate the extent of both primary and nodal disease. These significantly play a role in adequately staging patients from a clinical standpoint and this is supported by the Union for International Cancer Control (UICC) suggesting that any diagnostic information contributing to the overall accuracy of pretreatment assessment should be considered in the clinical staging.20

Note
The risk of second primary malignancy is decreased from 14.6% in patients with HPV-negative to 5.6% for patients with HPV-positive oropharyngeal cancers. Therefore, patients with HPV-negative disease require a panendoscopy as part of the standard workup and should have careful long-term (5-year) surveillance.

Positron emission tomography (PET)/CT can also be very useful in these patients not only to confirm location of primary and regional disease but also to help identify distant metastases as well as primary tumors in the instance of the unknown primary scenario (Fig. 11.3). PET/CT seems to be most useful when obtained prior to panendoscopy to help direct intraoperative biopsies. In one study, significantly more primary sites were found using this approach (37 vs. 27%).21 Perhaps, the biggest drawback with this technique is the false-positive rates of 39.3% in the tonsil and 21.4% at the base of tongue.22 However, high false-positive rates are acceptable when PET/CT is used to direct biopsies, as this ultimately results in fewer missed primary tumors. Therefore, PET/CT has become a useful adjunct in the detection of unknown primary lesions.

11.3.5 Pathology
HPV-mediated and nonmediated tumors have two distinct pathologic profiles. HPV-mediated tumors are generally poorly differentiated, basaloid, and nonkeratinizing, whereas HPV
nonmediated tumors tend to be well to moderately differentiated and keratinizing like other mucosal head and neck cancers.\textsuperscript{23}

Based on data from the National Cancer Database, 65% patients with oropharyngeal cancers presented with stage III or IV disease and disease-specific survival at 5 years was 46.1% not stratified for stage.\textsuperscript{24}

Nodal disease was generally found in levels II, III, IV in 80, 60, and 27% of cases with levels I and V harboring occult disease 7% of the time. For patients undergoing therapeutic neck dissections, however, levels II to IV remained highest in incidence, but levels I and V showed 17 and 11% risk of disease, thus arguing that comprehensive neck dissection should be performed in this cohort.\textsuperscript{25}

Distant metastases are present in about 14.6% of patients 3 years after presentation and overall survival at 3 years is 57.1%.

Note

HPV-associated carcinoma is often described as "poorly differentiated." This histological description is misleading because the characteristic deep blue histological staining does not imply poor differentiation or an aggressive biological behavior.
11.4 Human Papilloma Virus and Oropharyngeal Carcinoma

11.4.1 Introduction

Though the overall rate of head and neck cancer has remained stable or declined in recent decades, the incidence and prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has markedly increased.26 This is largely due to the emergence of the oncogenic HPV and its role in carcinogenesis—specifically, HPV16 infection, which accounts for 90 to 95% of all HPV-associated OPSCC and is now recognized as a dominant risk factor in the initiation of oropharyngeal cancer.27

A group in Finland first identified HPV in an oropharyngeal tumor cell line.28 In 1996, Dr. Maura Gillison, a researcher at Johns Hopkins Bloomberg School of Public Health, became interested in these new findings and began to expand on the data identified by those in Finland. While analyzing tumor samples they discovered HPV DNA in approximately 25% of the specimens.29 She also documented that the HPV DNA had integrated into the tumor cells and was producing two potent oncoproteins. They also were able to demonstrate a distinct molecular, clinical, and pathologic disease entity. Among their findings, HPV-positive OPSCC had characteristic basaoloid morphology, different patterns of cell mutations than seen in HPV-negative disease, and an improved disease-specific survival. This emerging viral-induced disease also differed from its HPV-negative counterpart with respect to risk factors, anatomical subsites, biological behavior, radiologic features, and overall prognosis.27

11.4.2 HPV Immunology

The virus itself is a nonenveloped double-stranded DNA oncovirus and fits within a group of over 100 related viruses that range from very-low-risk strains to the high-risk HPV 16 and 18. The two proteins responsible for carcinogenesis in high-risk subtypes are E6 and E7 proteins. E6 binds to p53 tumor suppressor protein and E7 binds to retinoblastoma, another member of the tumor suppressor family that contributes to regulating the cell cycle. The oncogenicity is based on a combination of genetic modifications including p53 degradation, retinoblastoma (Rb) protein downregulation, and p16 upregulation. Conversely, mutations caused by alcohol and tobacco demonstrates downregulation of p16 and upregulation of Rb. The upregulation of p16 is detected by immunohistochemical analysis and is used as a surrogate marker to detect HPV-mediated cancers.30,31

The lingual tonsils of the tongue base and palatine tonsils remain the principal subsites of this new disease entity. It is not fully understood why HPV16 has a subsite preference to the lymphoid tissue. It has been suggested that the invaginated tonsillar crypts may serve to facilitate viral capture and thereby provide access to the dividing basal cells.30,31,32 The crypts might effectively serve as a reservoir while protecting the virus from immune response.

11.4.3 Etiology

HPV-mediated oropharyngeal cancer is believed to be a sexually transmitted disease and studies have shown it to occur more commonly in younger patients of higher socioeconomic status who have had multiple sexual partners and have engaged more frequently in risky sexual behaviors.33 Other studies supporting the association between sexual behaviors and HPV-positive OPSCC is accumulating. In contrast, sexual behaviors are not associated with HPV-negative head and neck cancer reflecting the distinct etiology of these two diseases.34,35 High-risk behavior includes multiple sexual partners (25% increase with more than six partners), early age of first sexual experience, oral-genital sex, and a female partner with a history of an abnormal Pap smear.36 Smoking in adolescence has also been suggested to play a role in viral contraction.37

In contrast to HPV-negative oropharyngeal malignancy where the risk factors include tobacco and alcohol abuse, the risk factors associated with HPV-positive oropharyngeal carcinoma include multiple sexual partners, early age of sexual debut, multiple oral sexual partners, and a female partner with a history of abnormal Pap smear.

11.4.4 Clinical Presentation

Multiple studies have shown that HPV-positive tumors are more likely to present with early T stage (T1–T2) and higher N stage (usually cystic and multilevel) and have distinct histological features, such as moderate or poor tumor differentiation and nonkeratinizing or basaoloid pathology.34,35 Tumors tend to be small or occult with well-defined borders and cystic nodal metastases. Up to 90% of patients present with an asymptomatic neck mass.38

Conversely, HPV-negative tumors tend to be bulky with invasion into adjacent musculature.30,38,39 Further, distant metastases are seen to be lower in HPV-positive disease and occur later with different patterns of spread.30 Secondary primary tumor in patients with HPV-positive cancer is a rare occurrence and has proven to have an improved survival rate compared to patients with HPV-negative tumors.30,32,40

Note

The lingual tonsils of the tongue base and palatine tonsils are the principal subsites afflicted with HPV. The reticulated epithelium of the tonsillar tissue serves as a reservoir while protecting the virus from immune response.
11.4.5 Staging

The TNM classification set forth by the American Joint Committee on Cancer (AJCC) is the staging system used for OPSCC. There were no changes made between the sixth and seventh editions; however, it is expected that there will be changes with respect to HPV status in the eighth edition (> Table 11.1 and > Table 11.2).41

11.5 Treatment of Oropharyngeal Carcinoma

11.5.1 Historical Perspective and Nonoperative Treatment

Sir Edmund Burke once said, “those who don’t know history are destined to repeat it.” The great American author Mark Twain is quoted as saying, “history doesn’t repeat itself but it often rhymes.” These two intellects appreciate the need to know and understand the past to forge ahead to the future; this same tenet holds true for medicine. We must understand the past and the work that was done before us to help gain appreciation for where we are now and where we desire to go in the future.

The art of surgery has been practiced since and probably before the time of Hippocrates. The mainstay of cancer treatment for hundreds of years was and still is, in many cases, surgery. However, with its curative effects also brings morbidity. Within the head and neck these morbidities are manifested as cosmetic and functional both of which can have devastating effects on patients and their quality of life. The development of radiation therapy began in 1896 and has experienced much advancement over the last 100 years.43 The field of medical oncology has also seen advancements from nitrogen mustard for palliative treatment of cancer to targeted therapeutic agents.44 Oropharyngeal carcinoma for many years was treated with large and morbid surgeries that will be discussed later in this chapter, and this was the standard treatment modality.

Many advancements in radiation therapy were made in the mid-to-late 20th century. In 1970, Dr. Fletcher and his colleagues at the MD Anderson Cancer Center published an article that laid the foundation and defined the goals of radiation therapy in the head and neck. Although, this paper focused on the supraglottic larynx, it still demonstrated the benefits of postoperative radiotherapy and underscored that different subunits in the head and neck are truly different diseases. This paper proved to be the basis for conformal radiation therapy.

As radiation therapy techniques improved over time, the concept of organ preservation became the mantra of head and neck cancer treatment. Beginning with Dr. Wolfe and his colleagues at the University of Michigan and the Veteran Administration Laryngeal Study, the role of organ preservation in head and neck cancer treatment. Beginning with Dr. Wolfe and his colleagues at the University of Michigan and the Veteran Administration Laryngeal Study, the role of organ preservation in head and neck cancer treatment. Beginning with Dr. Wolfe and his colleagues at the University of Michigan and the Veteran Administration Laryngeal Study, the role of organ preservation in head and neck cancer treatment.

In 1994, a group of French physicians established the Groupe d’oncologique Radiotherapie Tete et Cou (GORTEC) trial. This was a randomized trial of stages III and IV oropharyngeal carcinoma that compared radiation alone versus radiation therapy with concomitant 5-fluorouracil and carboplatin. This study was very important in establishing the use of organ preservation therapy in oropharyngeal cancer. Despite boasting the increased benefit of the addition of chemotherapy to radiotherapy, increased toxicity was underscored as well. The 3-year overall survival for radiation alone was 31% compared to 51% for the chemoradiation therapy, but the incidence of grades 3 and 4 toxicities in the chemoradiation therapy group was 71% compared to 39% in the radiation therapy alone group. Important consideration should also be given to the fact that only 65% of the patients received all three cycles of the chemotherapy.

Pignon et al published a meta-analysis covering 63 studies and over 10,000 patients that discussed the added benefit of adding chemotherapy to radiation therapy in treating head and neck SCC. They documented an absolute survival benefit of 4% at 2 and 5 years with the addition of chemotherapy. They concluded that the routine use of chemotherapy in addition to radiation therapy is debatable and continued investigations were needed.48,49 Trends in the treatment of oropharyngeal cancer had already changed. There was a statistical increase in

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**Table 11.1 AJCC staging of oropharyngeal cancer**

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1X</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm but not &gt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease, tumor invades the larynx, deep/extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease, tumor invades the lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases the carotid artery</td>
</tr>
</tbody>
</table>

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**Table 11.2 AJCC staging of oropharyngeal cancer**

<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>Stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4a</td>
</tr>
<tr>
<td>Stage V</td>
<td>Any T (N3)</td>
</tr>
<tr>
<td>Stage V</td>
<td>Any T (N4)</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a (N0)</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T (N3)</td>
</tr>
<tr>
<td>Stage IV C</td>
<td>Any T (N4)</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T (N4)</td>
</tr>
</tbody>
</table>

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*Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.*
the use of chemoradiation therapy from 15% of primary treatment modality in 1985 to 29% in 2001. The use of surgery as a primary modality remained the same over this same time period around 27%.50

Technological advancements over time have led to the transition from radiation therapy being administered via two-dimensional radiotherapy to more directed treatment via the invention of conformal three-dimensional radiotherapy and intensity-modulated radiotherapy (IMRT).51,52 This has led to a more directed approach to treating the cancer and minimizing toxicity to the surrounding structures.53

As we look back in the history of the treatment of oropharyngeal cancer, it is important to point out that there is no current study comparing head to head in a randomized control fashion the two primary treatment modalities: surgery and radiation therapy. There are many studies comparing the use of different radiation therapy regimens, radiation with or without chemotherapy, radiation with different chemotherapy agents but no studies comparing it to surgery. Thus, the current approach to nonsurgical treatment of oropharyngeal cancer is in part because of anatomical organ preservation not necessarily preservation of organ function.

11.6 Surgical Management of Oropharyngeal Carcinoma

Surgery for oropharyngeal cancers takes on four main roles. The first role that surgery plays is to establish a diagnosis or to provide additional information to properly stage the cancer. The directed laryngoscope with base of tongue biopsy and ipsilateral tonsillectomy continues to play an essential role in workup oropharyngeal carcinoma. The second role is in the treatment of oropharyngeal cancer as a single modality or as the first stage for multimodality therapy for the primary and regional sites (neck dissections). The third role is to salvage the neck after radiation therapy or chemoradiotherapy, where there continues to be clinical or radiologic evidence of disease in the neck after definitive nonsurgical treatment. And finally, the fourth role for surgery is to treat both the primary and the neck in the salvage or recurrent setting after attempting organ preservation techniques.42

In the era of HPV-mediated tumors, the primary sites on presentation typically are T1 and T2 making them amendable to a transoral robotic resection. Open approaches continue to play a role for the management of advanced disease in patients who are not candidates for nonsurgical therapy or in patients with hard tissue invasion (cartilage or bone). The focus of surgical options in this chapter will be on open approaches to oropharyngeal carcinoma. Ford and colleagues presented a retrospective study of transoral robotic surgery (TORS) versus open surgery in the treatment of oropharyngeal carcinoma. They concluded that oncologic outcomes in OPSCC were not compromised by robotic surgical approaches, irrespective of HPV status. The same authors also demonstrated the efficacy of TORS in the salvage setting.24,50 Studies such as these prompted investigations that looked at the current role of open surgery for the oropharynx and other subsites in the head and neck.56 Open techniques in head and neck surgery have decreased with many citing the decline in head and neck cancer patients, the increased use of organ preservation techniques, and the increase of minimally invasive techniques. HPV-positive tumors are on the rise and are amenable to minimally invasive techniques; however, the role for open surgery still is the mainstay of salvage options for larger tumors and still should be considered in as first-line therapy for the appropriate selected patient.42,56

11.6.1 Transoral Approaches

The Trotter procedure is a median labiomandibular glossotomy, which as its name implies divides the lip, mandible, and the tongue in the midline to gain access to the base of tongue, soft palate, posterior pharynx, and nasopharynx. The main advantage is that it is midline thus preserving the bilateral mental nerves and thus preserving sensation.57 This method is very rarely used and has been taken over by the lip split and parasympathetic mandibulotomy (mandibular swing).58

The most common open approach to the oropharynx is through a lip-split incision and a midline, parasympathetic or lateral (to the mental foramen) mandibulotomy.58,59,60,61,62,63 This method increases exposure to allow the ablative surgeon to directly visualize the base of tongue down to the vallecula as well as allowing the reconstructive surgeon a wide field for inset of free tissue or regional flaps. This procedure results in a lot less edema of the tongue than the Trotter procedure.

1. The lip-split incision is designed to be contiguous with the neck incision. This can be accomplished with a midline lip split continuing down through the mentum to the neck and into a natural skin crease. This is also accomplished by making a stair-step midline incision through the lower lip and curvilinear incision around the mentum. This is extended down into a natural skin crease of the neck. Others favor a midline Z technique with the belief that this gives less tension over the chin and allows the skin tension line to lie in a different trajectory than the underlying muscle tension line. It also adds a geometric shape rather than a straight scar line62 (Fig. 11.4a–g).

2. Once the lip and the neck are open, the mandible is exposed. The surgeon has a choice to perform a midline, parasympathetic or lateral mandibular swing. The decision to choose the appropriate access is often determined by the location of the tumor, history of radiation fields, and most often the surgeon’s preference. The theoretical advantage of the parasympathetic approach is the preservation of the anterior belly of the digastric muscle, geniohyoid, and genioglossus muscles. By maintaining these muscles and their vascular supply, risk of necrosis, dead space, and subsequent infection all decrease. The midline also is a tighter space, thus often necessitating extraction of a central incisor. Most of the current literature would support the use of a parasympathetic approach.51,62,63
3. Once the location of the mandibulotomy is chosen, the surgeon must then decide on a vertical osteotomy through the mandible, a notched osteotomy, or a stair-step technique. The stair-step approach is the most commonly utilized approach given the ease of fixation and increased stability with fixation.61

4. Once the osteotomy is completed, the surgeon then must gain access to the tumor for extirpation. Incising the floor of mouth mucosa to assure an adequate amount of mucosa remains is the easiest and least morbid access to the oropharynx. Approximately a 1-cm cuff of mucosa should be left attached to the alveolar ridge for closure at the end of the case. The mylohyoid muscle must also be released deeply off the mylohyoid line of the mandible.

5. The tumor can be removed en bloc with the neck contents or can be sent off separately; however, we generally remove both specimens separately.

6. In most instances, this approach will require soft tissue reconstruction. Once this is completed, the mandible must be placed back into continuity. This can be accomplished with the use of a thick reconstructive plate, mini plates, or a lag screw. The stronger reconstructive plate is the one most often utilized due to its strength and durability.64

11.6.2 Trans-cervical Approaches

The transcervical approach is rarely used today in isolation, it is usually utilized with a transoral approach or with a TORS approach. The concern for clear tumor margins with a relatively blind entry into the pharynx was the most serious criticism of these approaches and that is the main reason they have fallen out of favor.

11.6.3 Anterior Pharyngotomy

The anterior pharynx can be entered via a suprathyroid or subhyoid approach. The suprathyroid approach to the oropharynx is best used for exposure of lesions of the base of tongue, tonsillar
arches, suprathyroid epiglottis, and low posterior pharyngeal wall lesions that cannot be excised transorally. The subhyoid approach is useful for lesions of the tongue base that have either directly invaded the hyoid bone, or have neck metastases that involve the hyoid bone.

11.6.4 Lateral Pharyngotomy

A lateral pharyngotomy approach is an approach that is seldom used in isolation. The pharynx can be entered high or low but place the lingual, hypoglossal, and superior laryngeal nerve at risk of injury. These approaches are commonly utilized with a mandibular swing or a TORS resection.

1. A low lateral pharyngotomy is performed in combination with a neck dissection.
2. The greater cornu of the hyoid bone is identified and exposed and the upper portion of the thyroid cartilage is identified and portion can be removed if additional access is required.
3. The mucosa of the pyriform sinus is elevated off the thyroid cartilage, and the pharyngotomy is performed.
4. As stated above, this approach is most utilized with a transoral approach and at our institution most often requires free tissue transfer for closure.

11.6.5 Combined Approach (Pull Through)

The pull-through procedure involves dropping the contents of the oral cavity/oropharynx into the neck by releasing these structures from their attachments to the mandible. This will give the ablative surgeon good access to lesions of the oropharynx. This technique can be utilized through an apron incision thus allowing intact lip sensation, better aesthetics, and an intact mandible thus avoiding the complications associated with making an osteotomy. Disadvantages include compromised exposure, loss of sensation over the floor of mouth and tongue bilaterally, and possible need for additional approaches to improve visualization (▶ Fig. 11.5).

1. Gain access to the neck and oral cavity via an apron incision that extends from mastoid tip to mastoid tip.
2. A bilateral level IA and IB neck dissection will be performed. This will allow identification of the hypoglossal nerve and many of the extrinsic muscles of the tongue.
3. With the hypoglossal nerve protected, the lingual mucosa of the floor of mouth is incised on both sides, taking care to leave a cuff of tissue on the mandible to facilitate closure. The lingual nerve and sublingual salivary gland are kept with the mandibular tissues.
4. The extrinsic muscles of the tongue attached to the mandible are incised and the tongue is pulled down anteriorly through the neck. Excision of the lesion is undertaken.

11.6.6 Approaches for Multiple Subsite Disease

Select large T3 and T4 tumors may require resection of multiple anatomical subsites. For example, when a base of tongue tumor extends inferiorly to involve the supraglottic larynx, a base of tongue resection and a total laryngectomy may be indicated. If the tumor has a superior extension into the oral cavity, a glossectomy may be indicated. On rare occasions, the tumor may extend superiorly and inferiorly necessitating a total glossectomy and total laryngectomy. The surgical exposure required for these extensive procedures often require a combine approach, a transcervical and a transoral approach with or without splitting the lip and the mandible. The location and the extent of the tumor determine the most appropriate exposure.

For T4 tumors invading into the mandible, a segmental mandibulectomy may be required. The approach is started by exposing the neck through a cervical exposure. This allows adequate exposure of the pharynx, safe exposure of the great vessels, and control of the margins. Often the best surgical sequence begins with a mandibular approach through a lip-split incision. This is followed by dissecting the skin, muscles, and the subcutaneous tissue off the mandible to expose the proximal and distal mandibular osteotomy sites. Once the
osteotomies are performed, the cancer-free mucosal margins should be confirmed.

11.7 Treatment of the Neck

The extent of the neck dissection is determined by the site of the disease, the extent of the nodal disease, and the patient’s prior treatment history. A level I neck dissection can be avoided in small lateralized primaries. Some surgeons perform a comprehensive neck dissection on all node-positive patients, while other surgeons will perform a comprehensive neck dissection but will leave the submandibular gland to prevent the risk of an orocutaneous fistula. In all cases of oropharyngeal malignancy, levels II to IV should be dissected in node-positive patients.42,70,71,72

Patients who demonstrate a well-lateralized primary may not require bilateral neck dissections; however, as disease approaches the midline, the surgeon should strongly consider treating bilateral necks.42

Extracapsular spread (ECS) has a significant impact on survival. In 1981, Johnson et al showed that patients with a single node less than 3 cm has only a 65% likelihood of ECS as compared to 75% of patients with nodes greater than 3 cm. ECS also has a significant impact on overall survival at 3 years. Oropharyngeal cancer patients without neck metastasis demonstrate an overall survival of 62%, while patients with neck disease but no ECS demonstrate an overall survival of 52%, and patients with ECS experience an overall survival rate of 28%. This was even after controlling for tumor stage, number of involved nodes, and tumor differentiation.73 The role of ECS in HPV-related cancer is controversial and currently under a lot of investigation.69

11.8 Complications of Treatment

Open surgical approaches are not without risk of complication and functional impact. Some effects of open approaches are a minor nuisance while others can be debilitating. Some of the most devastating complications are a result of injury to or sacrifice of the hypoglossal nerve which leaves patients with an immobile atrophic hemitongue with subsequent articulation and swallowing deficits. When osteotomies are performed, there is a risk of malunion, malocclusion (Fig. 11.6), and plate-related complications including infection and hardware extrusion. The oral mucosa can be denervated temporarily or permanently by damaging or sacrifice of the lingual nerve. The denervated pharynx can lead to a compromise in deglutition leading to aspiration.74,75

Radiation therapy, particularly when combined with chemotherapy, is associated with significant acute and late toxicities. Acute toxicities are side effects of treatment noted within 90 days of initiation of therapy, while late toxicity occurs after 90 days.76 Machtay et al reported 35% of patients who receive concomitant chemoradiation experience severe late toxicity.75 Generally, patients begin to experience the side effects of their therapy after the first 1 to 2 weeks of treatment; however, the level of toxicity varies between patients and the radiation dose. Some examples of acute toxicities include mucositis, dermatitis, edema, dysphagia, odynophagia, hoarseness, fatigue, pain, nausea, and vomiting. Common late toxicities include xerostomia, dysphagia, aspiration, feeding tube dependence, trismus, fibrosis, edema, and hoarseness (Table 11.3).76,77,78

Note

Extracapsular spread is responsible for a decline in overall survival of between 39 and 50% when compared with patients without evidence of neck metastases.
11.9 Psychosocial Concerns

While clinicians focus on curing tangible disease, it is important to consider the entire patient in treatment planning, especially psychosocial needs. Patients with head and neck cancers are particularly at risk for depression and anxiety. The proximity of cancer to vital structures may have a significant impact on breathing, speaking, chewing, swallowing, and overall appearance. In a report on the psychosocial care of patients with HPV-related head and neck malignancy, Gold discusses the progression of depression and anxiety through a patient’s battle with cancer.60 There are specific variables that significantly increase the risk of depression and anxiety in patients with head and neck cancer which include diagnosis age (<55 years), current employment at diagnosis, marital status, and loneliness.8 These characteristics particularly apply to patients suffering from HPV-related head and neck malignancy. Other factors such as concern about how the cancer developed and care of these often younger families may also contribute to an increased risk of depression during the treatment process.82

In many patients, depression is often present prior to a diagnosis and during the initial clinical presentation of malignancy.83 As patients begin therapy, anxiety is heightened; however, the level of anxiety decreases as patients respond to therapy. Conversely, depression increases during treatment due to increased personal dysfunction and the fear of recurrence, or even death, despite therapy. Several studies have looked at the effect of depression on treatment outcomes. Depression has been found to be a challenging but modifiable risk factor for malnutrition in patients undergoing radiation therapy.84 Lazure et al performed a randomized control trial comparing citalopram to placebo in order to prevent depression in patients being treated for head and neck cancer.82 They ultimately proved that patients who developed depression during therapy were significantly more likely to develop recurrence or die from their disease (p = 0.03).85

As patients progress through their treatments, particularly toward the end of therapy when toxicity is at its highest, depression levels peak. Nielsen et al showed that the addition of chemotherapy to treatment regimen of head and neck malignancy significantly increases the rates of depression, which is likely related to added toxicity.84,86 Frequently, patients suffering from depression prior to treatment experience continued depression posttreatment. Many of these patients fear recurrence after treatment, which leads to persistent depression and anxiety that do not subside until approximately 12 months posttherapy.

A randomized study was performed by Dr. Lydiatt and his group in Omaha, NE on the possibility of preventing depression in these high-risk individuals. This was a randomized study comparing the use of escitalopram to placebo in the treatment of nondepressed patients. The administration of escitalopram had a drastic and statically significant reduction in patients developing depression (25% in placebo and 10% in treated). In our practice, we routinely prescribe escitalopram 10 mg for 1 week and increase to 20 mg on the second week and treat until 3 months posttreatment.
Open Management of Carcinoma of the Oropharynx

11.10 Conclusion

The management of cancer of the oropharynx has experienced a significant change over the past decade as HPV-associated disease has gained prevalence. The emergence of HPV-associated disease will require a rethinking of the current staging system and the treatment options. Open surgical approaches to the oropharynx are not commonly performed given the advancements in radiation therapy and the popularization of TORS. Open surgical approaches to the oropharynx remain an important aspect of contemporary therapy. Although more commonly applied to salvage therapy, open surgical approaches may provide an exposure advantage that can be helpful in achieving en bloc resection and reconstructive flap inset. The transmandibular, transcervical, and the pull-through approaches each offer advantages and disadvantages. The ablative surgeon should be comfortable with each approach and understand the limitations of each approach. The more diverse a surgeon’s “tool box” of surgical approaches, the more likely that a safe resection can be achieved with limited morbidity.

References


Note

Evidence exists to demonstrate that the administration of anxiolytics has a significant and statically significant reduction in patients developing depression.
Open Management of Carcinoma of the Oropharynx


12 Transoral Robotic Management of the Oropharynx

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12.1 Introduction

Robotic surgery represents a revolutionary approach to minimally invasive surgery. Robots are often thought of as a cutting edge and novel concept, and though there is much truth to this assertion, the idea of robots and their ability to assist with human progress has been around for at least a century. Though Isaac Asimov is traditionally heralded as the first to popularize the term robotics and bring the idea of robots to the collective minds of scientists, physicians, and the greater society in the 1940s in his collection of short stories called Roundabout, many credit Karel Capek of coining the phrase “robot” in his short story Opilé in 1917. In Opilé, Capek used the term robot, which comes from the Czech word robota, which roughly translated to laborer or serf in English.

Indeed, humans have come a long way from the fictional writings of Capek, Asimov, and many others by turning the concept of robotics into functional entities. Many fields have seen a robust increase in the use of robots, including medicine. The application of robots in medicine has paralleled the trend of minimally invasive surgery. Minimally invasive procedures have the potential to improve outcomes while decreasing surgical morbidity and mortality, and technological advances have helped physicians to achieve these goals.

Significant enhancements in minimally invasive instruments came in the 1980s with major advances in computing and microelectronics coupled with advancements in surgical technology, knowledge, and technique. Laparoscopy had been described previously when Dr Kurt Semm performed the first laparoscopic appendectomy in 1983. This achievement was in large part due to advances in endoscope technology, coupled with advances in charge-coupled devices necessary for digital imaging and video displays. Soon after, the first laparoscopic cholecystectomy was performed in 1985, marking the beginning of more modern laparoscopic techniques. This newly expanded field of minimally invasive surgery also brought with it the realization of the limitations of laparoscopic approaches in performing more complex procedures.

To many, robotic surgery served as one answer to expanding minimally invasive techniques to surgery. By definition, robotic surgery employs the use of a powered device that, under computerized control, manipulates instruments to perform a surgical procedure. Though there were examples of robotic surgery previously (notably work by the military and NASA program), the first Food and Drug Administration (FDA)-approved robotic device was used in 1993 in abdominal surgery and was called the automated endoscopic system for optimal positioning (AESOP). AESOP consisted of an articulating arm that was table-mount and was used to control the movement of the laparoscopic camera by hand or foot controls. The ZEUS robot represented another leap in the field as it was voice controlled and tremor filtering. The da Vinci also has exchangeable sterile components, a console designed to decrease fatigue, and had the ability to hold a variety of instruments that were controlled with joysticks by the surgeon, and was first used in 1998. Of interest, in September of 2001, Dr. Jacques Marescaux in New York, United States used the ZEUS system to perform a robot-assisted cholecystectomy on a patient 2,485 mi away in Strasbourg, France which represented the first trans-Atlantic telerobotic surgery.

The next major advance in robotic surgery was the invention of the da Vinci robot (Intuitive Surgical, Inc., Sunnyvale, California, United States), which first became commercially available in Germany in 1997. In the da Vinci system, the three-dimensional (3D) screen is designed to represent a natural extension of the surgeon’s eyes and the seven degrees of freedom allowed the surgeon to mimic open surgery by allowing for natural eye-hand instrument alignment. The da Vinci also has exchangeable sterile components, a console designed to decrease fatigue, and tremor filtering. The da Vinci allowed for extension of robotic surgery into several surgical fields, including otolaryngology, head and neck surgery.

Perhaps the first instance of robotics in otolaryngology was in 2002 when Haus et al performed experiments with the da Vinci robot on animals demonstrating that robotic endoscopic surgery of the neck was feasible and may offer several advantages to open approaches. In 2005, Mcleod and Melder described the first human application of robotic surgery in the field of otolaryngology with the excision of a vallecular cyst. Then, based on previous work with their own animal models and of studies by other groups, Hockstein and colleagues demonstrated in a cadaveric model that transoral robotic surgery (TORS) provided an excellent 3D visualization and allowed for adequate instrument access in order to successfully resect base of tongue lesions. O’Malley et al then reported the ability of TORS to successfully gain great visualization of structures of the oropharynx. These studies ushered in the era of TORS as being a feasible way to access certain oropharyngeal and hypopharyngeal structures by proving that traditional transmandibular or transcervical approaches, and their associated morbidity, were not necessary for a variety of head and neck surgical procedures. As such, in 2009, the FDA approved the use of the da Vinci for TORS of the larynx and pharynx, including the oropharynx.

As is apparent in the literature as well as in clinical practice, there has been rapidly increasing interest in TORS. This interest is likely linked to the fact that robotic minimally invasive approaches to the oropharynx have been shown in various studies to be associated with an acceptable safety profile, comparable oncologic results, superior functional outcomes as well as the potential for de-escalation of adjuvant therapy for oropharyngeal cancer, thereby decreasing long-term morbidity.

Given the exciting expansion of TORS in the treatment of oropharyngeal cancer, the purpose of this chapter is to discuss the epidemiology and etiology of the disease, anatomy of the oropharynx, staging, clinical presentation, diagnosis, workup, and presentation of case studies from the perspective of transoral robotic surgical techniques in oropharyngeal cancer.

12.2 Epidemiology of the Disease

In the United States alone, over 5,000 new cases of oropharyngeal cancer are diagnosed annually. Of these cases, over 85% of...
the cancers are squamous cell carcinomas (SCCs).13 Worldwide, there has been a significant increase in the incidence of oropharyngeal cancer from 1983 to 2002, predominantly in developed countries. Significant increases in the incidence of oropharyngeal cancer in the United States, Canada, Japan, Australia, and Slovakia have been observed among men. In women, significant increases have been seen in Denmark, France, Estonia, the Netherlands, Poland, Slovakia, Switzerland, and the United Kingdom. Moreover, in men, there was a significantly higher increase in oropharyngeal cancer in patients younger than 60 years compared to older patients in the United States, Australia, Canada, Slovakia, the United Kingdom, and Denmark.14

This increased incidence of oropharyngeal cancer has been attributed to chronic infection with high-risk subtypes of HPV. This is supported by the observation that DNA of oncogenic HPV, particularly HPV16, is detected in approximately 26% of worldwide head and neck SCCs and the majority of oropharyngeal squamous cell carcinomas (OPSCCs).15 Molecular evidence for HPVs’ role in oropharyngeal cancer has been more definitively elucidated, in that viral integration and expression of E6 and E7 viral oncogenes (which inactivate tumor-suppressor proteins p53 and pRb) have been shown. The annual number of HPV-positive oropharyngeal cancers has increased dramatically, with one study citing as much as a quadrupling of the number of cases from 1970 to 2007. Cancers of the base of tongue are more often poorly differentiated in contrast to other sites, with as many as 60% being high grade in nature, though this number is significantly less in HPV-positive tumors, and the histological grade may be less relevant in HPV-related disease as many tumors appear to be basoloid poorly differentiated tumors, despite a well-documented improved prognosis.

It was found that HPV infection increases the risk of developing oropharyngeal cancer by 32-fold compared to an increased risk of 2.5-fold with drinking and threefold with smoking.17 It should be noted that there is debate regarding the synergistic effect of exposure to HPV coupled with alcohol and/or tobacco use, with some studies finding some evidence of a synergistic effect while others finding none.16,19 The increase in the incidence of HPV-positive oropharyngeal cancers varies by subsite. Tonsillar cancer and base of tongue cancer are the two most common oropharyngeal subsites, accounting for 90% of all OPSCC. Tonsillar cancer is the most common oropharyngeal subsite.20 It has been reported that from 1970 to 2007 there was a cumulative sevenfold increase in the number of HPV-positive tonsillar tumors, a finding that represented a doubling each decade in the incidence.21 In the base of tongue, HPV-positive cancers increased by 30% from 1998 to 2007. Cancers of the base of tongue are more often poorly differentiated in contrast to other sites, with as many as 60% being high grade in nature, though this number is significantly less in HPV-positive tumors, and the histological grade may be less relevant in HPV-related disease as many tumors appear to be basoloid poorly differentiated tumors, despite a well-documented improved prognosis.

Other factors other than HPV exposure have also been found to have a relationship to oropharyngeal cancer. In a study of 100 patients newly diagnosed with oropharyngeal cancer from 2000 through 2005, the researchers found that patients with a first-degree relative with head and neck, a history of cancer in a sibling, a history of oral papillomas, and poor oral hygiene were all associated with oropharyngeal cancer.22 Interestingly, it was also noted that regular marijuana use had an association with oropharyngeal cancer. The potential causality of many of these observed associations remains unknown.

Even with standardized treatment and controlling for stage and histological features of the tumor, treating physicians often find it difficult to predict outcomes. It is known, however, that HPV-positive oropharyngeal cancers have a better clinical outcome than HPV-negative cancers in general.22,23 In a retrospective analysis looking at the survival of patients with stage III or IV OPSCC the investigators found that the 3-year survival of patients with HPV-positive tumors had an 82.4% rate of overall survival while those with HPV-negative tumors had a significantly lower survival rate of 57.1%.24 The superior survival seen in HPV-positive oropharyngeal cancers can be attributed to the hypothesis that HPV-positive and HPV-negative squamous cell carcinomas are distinctly different diseases and have different causes.25 These differences between viral positive and viral negative disease have not been fully elucidated and currently remain the topic of significant research.

## 12.3 TORS Anatomy of the Oropharynx

The TORS surgeon approaches the complex anatomy of the oropharynx in a way that is vastly different than the more
traditional external approach, an aspect of robotic surgery that can be quite challenging, particularly for a novice. In general, surgeons are more familiar with lateral-to-medial surgical approaches (in anatomical terms), and therefore somewhat of a paradigm shift must be made by the surgeon in order to perform minimally invasive robotic surgery which is approached “inside out” so to speak. Poor anatomical knowledge and limited transoral robotic experience can thus be a source of major morbidity. This section discusses the important anatomical considerations of the transoral approach to the oropharynx, including a discussion of the limits of the tonsillar fossa and base of tongue in relation to important muscles, nerves, and arteries.

Anatomically, the tonsillar fossa is framed anteriorly by the palatoglossus muscle and posteriorly by the palatopharyngeus muscle, the pair forming the tonsillar pillars (Fig. 12.1). Of note, the anterior tonsillar pillar borders the retromolar trigone and extension of tumor to the retromolar trigone can occur because of the lack of substantial tissue between the tonsillar fossa and retromolar trigone. Once tumors violate the constrictor muscles, the path of least resistance is extension into the parapharyngeal space. It is also important to note that resection of tumors extending to the retromolar trigone from the tonsillar fossa increases the risk of lingual nerve injury as the nerve is closely approximated to the anterior border of the medial pterygoid muscle.

The deep limit of the tonsillar fossa is marked by the pharyngobasilar fascia and the underlying superior pharyngeal constrictor muscle. Therefore, the deep surface of the pharyngeal constrictor muscles represents the deep (or most lateral) margin for TORS radical tonsillectomy. As such, the styloglossus muscle runs in the intrinsic longitudinal lingual muscle fibers while inferiorly the stylohyoid ligament inserts on the hyoid bone. Often this region, as well as the lateral glossotonsillar sulcus and base of tongue are the inferior limits of the resection for tonsillar cancers during TORS.

From an embryological and anatomical perspective, the base of tongue can be divided into an oral portion and pharyngeal portion. Robotic surgeons are generally more interested in the pharyngeal portion, or the portion posterior to the circumvallate papilla, as this is the base of tongue. Lingual tonsillar tissue is embedded in the epithelium of the base of tongue and this lymphoid tissue is in continuity with the palatine tonsils. Of note, the genioglossus muscle is an important landmark as deeply invasive tumors that invade the root of the base of tongue become difficult, if not impossible, to access transorally and resect with appropriate margins. Similarly, it is difficult to achieve adequate exposure for tumors with significant anterior extension into the tongue and obtaining adequate margins in such cases can also be problematic. Additionally, significant muscular involvement of the tongue significantly impacts functional outcomes, especially when surgical resection is followed by adjuvant therapy.

An anatomical understanding of the course of the lingual artery is essential during TORS surgery to avoid significant bleeding while dissecting at the base of tongue. The lingual artery, a branch of the external carotid artery (ECA), runs in an anteromedial direction toward the lateral base of the tongue (Fig. 12.2). Along its course, the lingual artery runs posteriorly to the greater cornu of the hyoid bone and may form a loop between the styloglossus muscle and the hyoid bone. Of note,
the area where the lingual artery passes on the superior surface of the hyoid bone is considered to be most vulnerable to injury during the TORS procedure.\textsuperscript{30} The artery runs deep to the middle pharyngeal constrictor muscle and subsequently between the posteroinferior segment of the stylohyoid ligament. At this point the lingual artery branches into three components. The three components are the dorsal lingual artery, which passes to the dorsum of the tongue, the sublingual artery, and the artery profunda linguae, which passes between the intrinsic tongue musculature and genioglossus muscle. Therefore, based on the course of the artery, the TORS surgeon can avoid injuring the artery by being very careful to limit dissection medial to the course of the artery, the TORS surgeon can avoid injuring the artery by being very careful to limit dissection medial to the styloglossus muscle and the stylohyoid ligament.\textsuperscript{30}

**Note**

The lingual artery, a branch of the ECA, runs in an anteromedial direction toward the lateral base of the tongue. The area where the lingual artery passes on the superior surface of the hyoid bone is considered to be most vulnerable to injury during base of tongue surgery.

In cases of tumor extension necessitating dissection in this area, ligation of the lingual artery during ipsilateral neck dissection may be considered depending on the surgical sequence preferred by the surgeon. Bleeding from the lingual artery during TORS procedures can be quite brisk, and is generally controlled via ligature clips, or suction electrocautery.

The hypoglossal nerve is also in the surgical field and at risk during TORS surgery. The hypoglossal nerve classically runs between the internal carotid artery (ICA) and internal jugular vein while running superficial to the vagus nerve. The nerve then passes on the surface of the hypoglossus muscle and superior to the hyoid bone. The hypoglossal nerve passes deep to the digastric and mylohyoid muscles, and it is at this junction that the robotic surgeon must exercise great care as this is where the nerve is at highest risk as it passes superiorly toward the oral cavity. Finally, the hypoglossal nerve splits into several branches between the mylohyoid and genioglossus muscles and these represent terminal branches.

The robotic surgeon must also be mindful of the glossopharyngeal nerve. After passing between the internal jugular vein and ICA, the nerve descends superficial to the ICA. Cranial nerve IX curves around the stylohyoid muscle and runs along with the muscle until passing between the superior and middle pharyngeal constrictor muscles. The TORS surgeon should be mindful of the anatomy of the glossopharyngeal nerve as the nerve can branch within the tonsillar fossa and typically these branches run posteroinferiorly in the tonsillar fossa heading toward the base of tongue. During deeper TORS pharyngeal resections for more advanced tonsillar cancers, the nerve can be injured.

For obvious reasons, the carotid artery is of particular significance during transoral surgery. The cervical portion of the ICA begins at the bifurcation of the carotid artery into the ECA and ICA. The ICA is posterolateral to the ECA as it ascends, moving posteromedial to the ECA as it courses to the skull base without any branches. By adulthood, the distance from the ICA to the tonsillar fossa is 2.5 cm and therefore injury to the artery is possible.\textsuperscript{31} In most cases, blunt dissection lateral to the pharyngeal constrictors can be performed safely. Important landmarks for identification of the ICA are the styloglossus and stylopharyngeus muscles. The styloglossus muscle at its origin is lateral to the ICA and courses medially to become medial to the ICA at the oropharynx. The stylopharyngeus is also medial to the ICA at the level of the OP. Therefore, both the styloglossus and stylopharyngeus muscles can be transected as long as there is a known pharyngeal fat pad protecting the ICA from transection.\textsuperscript{32} Though textbooks often cite a straight path of the ICA, studies have shown deviated courses of the artery as well. The ICA is reported to have variations in its anatomical course in 6 to 30% of patients, with one study citing as high as 62% of patients having ICA variations.\textsuperscript{33} In general, these variations have no clinical bearing; however, with an aberrant ICA that is in direct contact with the pharyngeal wall, injury to the artery during TORS is a serious concern during tonsillectomy.

It is reported in one study that approximately 8% of patients showed potentially dangerous variations in the course of the ICA, defined as having a direct submucous trajectory of the artery with no separating fat pad between the pharyngeal wall and the artery and/or asymmetry of the lumen of the vessel.\textsuperscript{34} These patients with what some describe as an ICA with a “dangerous loop” are at increased risk for injury to the ICA during transoral surgery. Patients with a retropharyngeal carotid artery or other arterial variations are at high risk of ICA injury and thus represent a population of patients that may have anatomical contraindications for TORS. Elderly patients have even greater coiling or tortuosity than younger patients\textsuperscript{35} and men have a higher incidence than women of ICA abnormalities.\textsuperscript{36} In the elderly, abnormalities of the ICA have been linked to hypertension and atherosclerosis, and are thus acquired changes.\textsuperscript{37} Advances in technology, including ultrasound, angiography, and computed tomography (CT) scanning have increased the ability to detect abnormalities in the ICA; however, patients are often asymptomatic and thus the finding is usually incidental.\textsuperscript{38} Patients with velopharyngeal insufficiency have also been found to have a higher incidence of an aberrant course of the ICA, in particular syndromic patients in whom the ICA is medialized. For instance, velocardiofacial syndrome is known to cause a change in the carotid anatomy such that the artery is more tortuous or has more coiling than other patients.\textsuperscript{39} Neurofibromatosis type 1, Prader–Willi syndrome, Turner’s

**Note**

The distance from the ICA to the tonsillar fossa is 2.5 cm on average. Important landmarks for identification of the ICA are the styloglossus and stylopharyngeus muscles. In addition, anatomical variations of ICA may increase the risk of injury.

**Note**

Resection of advanced tonsillar cancers may place the glossopharyngeal nerve at risk as the nerve courses around the stylopharyngeus muscle and runs along with the muscle until passing between the superior and middle pharyngeal constrictor muscles.
syndrome, and Saethre-Chotzen syndrome have also been found to have potentially higher rates of ICA variations\(^40\) (\(\Rightarrow\) Table 12.1).

### Table 12.1 Syndromes associated with aberrant internal carotid artery

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<td>Velocardiofacial syndrome</td>
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<td>Neurofibromatosis type 1</td>
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<tr>
<td>Prader-Willi syndrome</td>
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<td>Turner’s syndrome</td>
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<td>Saethre-Chotzen syndrome</td>
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One can conclude that patients with variations in the course of the ICA are at increased risk for devastating complications during transoral surgery. It is therefore important to note aspects of the patient’s medical history that increase the risk of aberrant ICA courses. In addition to careful examination of preoperative imaging that is warranted in all TORS candidates, meticulous surgical technique is required to prevent devastating internal carotid injury.

The ECA also can show variations, though cadaveric studies have shown ECA variation to be rare and in the minority of specimens.\(^{20}\) Normally the ECA is just under 2 cm lateral to the lateral pharyngeal wall. In the vast majority of patients, the ECA runs deep to the styloglossus muscle. Therefore, dissection deep to the styloglossus muscle during a transoral approach to the oropharynx can lead to injury to the ECA. However, in a minority of patients, the ECA runs through a dehiscence in the fascial plane between the stylopharyngeus and styloglossus muscle. In this sense, in patients with this dehiscence, the ECA is close to the pharyngeal constrictors, exposing it to injury.

### 12.4 Clinical Presentation

#### 12.4.1 Local Disease

Tonsil cancer may present as either an exophytic tumor or endophytic ulcer. It may involve the anterior tonsillar pillar and occasionally extend to the posterior pharynx or palate in more advanced cases. Asymmetry or irregularity of the tonsil may be a sign of cancer. A foul odor can often be associated with them if there is a superinfection. Other signs include sore throat that does not respond to medical therapy, globus sensation, dysphagia, otalgia, trismus, or muffled voice. It should be noted that often, early-stage tonsillar cancers are occult, quite small, and hidden within the tonsillar fossa. Interestingly, tobacco-related oropharyngeal cancer tends to present with odynophagia, however, HPV-associated oropharyngeal cancer is often asymptomatic. It is not uncommon for the initial presenting sign of HPV-associated carcinoma to be a metastatic cervical lymph node.

Similarly, base of tongue cancer can be difficult to diagnose given that it is difficult to visualize the base of tongue on physical examination as well as the fact that lingual tonsil tissue has less vibrant sensory innervation. Early-stage tumors are often located within the lingual tonsil tissue and frequently asymptomatic. As the tumor progresses, symptoms may include globus sensation, sore throat, dysphagia, difficulty with articulation of speech, difficulty breathing (very advanced disease), and ear pain.

Soft palate cancers or cancers of the posterior pharyngeal wall are generally readily noticed on physical examination and often present with the patient complaining of sore throat, dysphagia, or dysphonia, or referred ear pain.

### 12.4.2 Regional Disease

The lymphatic drainage of the oropharynx, as with other areas of the head and neck, is often very predictable, and an important consideration in transoral oropharyngeal management. Level I lymph nodes are generally considered to be at very low risk with oropharyngeal cancer. However, given the anterior tonsillar pillar’s proximity to the oral cavity, some have argued that these tumors are at risk for level I metastasis.\(^41\) That being stated, the majority of oropharyngeal cancers spread predominately along the jugular lymphatic chain, which constitutes lymph nodes in levels II, III, and IV\(^42\) (\(\Rightarrow\) Fig. 12.3). Studies have shown that lymphatic drainage from the tonsil is mainly to level II nodes though level III or IV nodes are also at risk.\(^43\) Tumors approaching midline, or with significant palatal involvement have a predilection for retropharyngeal lymph nodes (sometimes bilaterally), and therefore these nodes must be evaluated with imaging preoperatively, and managed appropriately. Base of tongue cancers have a tendency to metastasize to bilateral jugular lymphatic nodes involving levels II, III, and IV (\(\Rightarrow\) Fig. 12.4).

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<td>HPV-associated oropharyngeal cancer is often asymptomatic and as a result HPV-associated carcinoma commonly presents with a metastatic cervical lymph node as the initial clinical sign.</td>
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The HPV status has a significant effect on the risk of regional disease in oropharyngeal cancer. It has been noted that patients...
with HPV-positive oropharyngeal cancer often present with a neck mass (~90%), while HPV-negative patients typically present with dysphagia or odynophagia. Some have speculated that patients with HPV-positive disease have papillomatous disease that is initially less symptomatic because it is more superficial. As a result, these patients may not present until the disease has spread to the neck. In contrast, HPV-negative disease presents with a larger painful tumor, frequently with ulceration at the primary site and they more commonly complain of odynophagia at presentation (▶ Fig. 12.5a, b).

**Note**

While patients with HPV-positive disease may present with bulky disease that is not painful, patients with HPV-negative disease more often present with a painful ulcer.

Extracapsular extension (ECE) has been shown to be a poor prognostic factor in multiple studies, and is associated with regional recurrences, nodal metastases, and distant metastases. ECE in HPV-related oropharyngeal cancer does not appear to have the same impact clinically. This was confirmed in a recent study of 137 patients with oropharyngeal cancer with cervical lymph node metastases and known ECE status, it was found that ECE was not associated with worse disease-specific survival among p16-positive or p16-negative oropharyngeal cancer patients. The authors noted that in the p16-negative cohort, there was a higher correlation with survival based on the number of lymph nodes rather than the presence of ECE. The impact of ECE in the setting of HPV-positive disease remains a topic of ongoing research.

Radiographically, matted lymph nodes, or two or more nodes in contact with one another that do not honor the intervening fat planes, have been identified as a poor prognostic factor in HPV-positive oropharyngeal cancer. Matted nodes are associated with a poor prognosis even independent of T, N, or smoking status. More specifically, matted nodes have been noted to represent an increased risk of distant failure. There is, however, continued debate regarding matted lymph nodes and their impact on locoregional recurrence. Some studies suggest that the matted lymph nodes do not increase the risk of regional recurrence. One study found patients with HPV-positive disease and matted lymph nodes demonstrated a 60% greater risk of distant failure than HPV-positive patients without matted nodes; however, matted nodes did not increase the risk of regional recurrence in either group. These findings and the impact of matted lymph nodes on risk stratification are important factors that need to be elucidated to determine responsible de-escalation protocols.
Note
In patients with HPV-associated disease, matted lymph nodes are associated with a poor prognosis independent of T, N, or smoking status. While it is not clear that matted nodes increase the risk of regional recurrence, they do increase the risk of distant metastasis.

12.4.3 Distant Disease
The incidence of distant metastasis in OPSCC is relatively high. The reported rate of distant metastasis of OPSCC irrespective of treatment modality is 15 to 20%.54 It is commonly accepted that locoregional control of oropharyngeal cancer has continued to improve. Therefore, the pattern of recurrence is shifting to distant sites and distant metastasis in OPSCC has become an increasingly more relevant problem. It can be argued that a paradigm shift is well under way with the focus shifting from control of locoregional disease55 to the implications of distant metastasis.

Note
Control of the primary and regional sites has improved and as a result, the pattern of recurrence is shifting to distant sites.

In general, malignancies either have a tendency to spread via lymphatic and/or hematogenous mechanisms. The method in which a cancer metastasizes is a function of tumor type and tumor biology and the metastatic potential of a given tumor often has great implications on overall survival. Previously, it was generally considered that all head and neck squamous cell carcinomas, including OPSCC, spread primarily via a lymphatic mechanism as evidenced by the tendency for aggressive tumors to metastasize to lymph nodes in the neck.28 OPSCC is usually caused by environmental factors such as tobacco and alcohol, almost exclusively spreads via lymphatic spread.26 In contrast, HPV-associated disease seems to spread via both a lymphatic as well as a hematogenous pattern. The revelation that HPV-induced OPSCC behaves differently from HPV-negative tumors has resulted in significant research examining mechanisms of metastases.

Published reports increasingly raised concern that HPV-related malignancy demonstrates unusual patterns of metastasis and was considered by some to be an “explosive disease,” thus bringing into the fore that a phenotype exists within the normally well-behaved malignancy that had outlying characteristics.57 Studies emerged showing strange behavior in p16-positive tumors as they were increasingly being found in “strange” places, including a case report discussing an OPSCC that tested positive for p16 that was found in the lumen of the internal jugular vein.58 Case reports like this strengthened the concept that HPV tumors spread hematogenously. Cellular research seems to also support the idea of OPSCC spreading through the bloodstream. Data indicate that vascular endothelial growth factor (VEGF), a potent angiogenic factor found in many cells particularly those that promote the growth of blood vessels, plays a role in HPV-related disease. Studies have shown that the HPV oncoprotein E6 directly stimulates the VEGF gene without p53 stimulation. In particular, there is a correlation in head and neck SCC between both elevated vasculature in tumors and distant metastasis in patients with higher VEGF-C levels.59 These studies have given a molecular basis to the concept of p16-positive OPSCC spreading hematogenously.
Consequently, the concept of hematogenous spread of HPV-related OPSCC may explain its nontraditional metastatic patterns. It has been found that patients with p16-positive OPSCC had a significantly longer delay in the development of distant metastasis when compared with p16-negative patients. Furthermore, patients who undergo surgery for management of p16-positive OPSCC experienced a decreased rate of distant metastasis coupled with a longer time. These observations are believed to be a result of locoregional control and the antitumor properties associated with the disease-mediated inflammatory process. HPV-negative patients treated with chemoradiotherapy experienced a higher rate of distant metastasis after treatment when compared with patients with HPV-positive disease. In addition, p16-positive tumors also behave differently in their pattern of metastasis. Reports exist of OPSCC staining positive for p16 being found in the kidney, skin, intra-abdominal lymph nodes, central neck nodes (level VI), muscle, and brain.

Note

Data suggest that HPV-associated OPSCC spreads through hematogenous dissemination, therefore explaining its nontraditional metastatic patterns. This data may support the need for systemic surveillance programs.

Of particular concern, OPSCC disseminating to the brain has been of great interest and research strengthens the notion of the ability of OPSCC to spread via a vascular mechanism. The central nervous system (CNS) lacks any sort of lymphatic drainage. As such, the only way for metastatic cancer cells to enter the CNS is by passing through the blood–brain barrier. The literature on tumors known to spread hematogenously, including lung cancer, breast cancer, and melanoma, shows that these tumors are the most common tumors which manifest brain metastases. It has been noted that the vast majority of head and neck SCCs that metastasize to the brain, though admittedly a small population, have been p16 positive. Furthermore, some patients with p16-positive brain metastasis were found in one study to have late metastases with a range of 19 to 57 months after primary treatment. Even in more common sites like the lungs, which have been found in the literature to be the most ubiquitous distant metastatic organ for OPSCC and has also been found to be present equally in both p16-positive and p16-negative tumors, have strange presentations in HPV-positive OPSCC. Atypical CT scan findings have been reported in patients with p16-positive pulmonary metastases, another aspect of HPV-related OPSCC that supports hematogenous spread. Cancers that are hematogenously spread to the lungs generally are characterized as being multiple, bilateral, and variable sized as opposed to the lymphatically spread tumors that diffusely thicken the pulmonary interstitium. Interestingly, it has been found that it is very rare for patients with p16-negative cancers metastatic to the lungs to present with multiple, bilateral nodules of variable sizes while this radiographic finding has been observed in p16-positive head and neck SCC. This abnormal finding of p16-positive tumors metastatic to the lungs underscores the metastatic behavior of p16-positive OPSCC as well as supports the concept that these cancers disseminate hematogenously.

Note

The metastatic pattern and mechanism of metastases in HPV-related SCC appear to have an increased potential for hematogenous spread as compared to the HPV-negative counterpart.

Certainly the current management paradigm of transoral surgery followed by adjuvant radiation is in striking contrast with what we now know about the ability of these tumors to metastasize. Therefore, while transoral modalities may be appropriate for early-stage disease, caution must be exercised when extrapolating data, techniques, and treatment options for more advanced cases due to the risk of distant metastasis. Further data are needed to understand how to apply the current de-escalation strategies proposed for HPV-related OPSCC.

12.5 Surgical Treatment

12.5.1 Indications and Oncologic Outcomes

The indications for TORS vary slightly from center to center. From a technical standpoint, adequate transoral access to the oropharynx is paramount. Patients with microglossia or trismus present a challenge for exposure and may not be appropriate candidates for transoral surgery. Studies have examined the hyoid-mental length, mandibular body height, and neck circumference in conjunction with the incisive opening to determine the feasibility of the transoral approach, yet no single measurement has proven reliable in determining transoral access.

A strong prognostic factor in determining the likelihood of success of TORS is staging. As mentioned previously, patients have better disease-free survival with TORS in T1 and T2 lesions as compared with more advance tumors, though it should be noted that T3 and T4 tumors may be amenable to TORS and later staged tumors have been shown to be appropriately resectable via TORS. Nevertheless, the technical ability to resect an advanced-stage tumor does not alter the biology of the disease and caution must be exercised as previously noted. Staging determinations when examining patients for TORS candidacy should be viewed in light of the current controversy in staging in HPV-related tumors. It should also be noted that significant changes to the current staging systems are on the horizon for HPV-related disease, due to the striking differences in this disease compared to HPV-negative disease.

Note

Measurements such as the hyoid-mental length, mandibular body height, and neck circumference in conjunction with the incisive opening are not reliable in determining the feasibility of the transoral approach.

Location of the tumor also plays an important part in determining if a patient is suitable for a transoral approach, particularly
in higher-staged tumors. Tumors that arise from the tonsillar fossa or the base of tongue, particularly the lateral tongue base, generally have more favorable features for TORS surgery compared to deeply infiltrative or larger midline base of tongue tumors. Exophytic tumors are generally excellent candidates for TORS compared to more infiltrative patterns. As noted previously, deeply infiltrative tongue tumors are not good candidates for transoral surgical management due to issues related to obtaining negative margins, and functional sequelae of surgical resection of significant portions of the tongue musculature. Conversely, tumors of the soft palate are often best managed with traditional approaches because they are often faster and less costly. Some have advocated that tumors of the soft palate have a relatively higher risk of velopharyngeal insufficiency and nasopharyngeal reflux and may be better treated with nonsurgical options. At our institution, we have found that soft tissue reconstruction provides patients with an excellent functional restoration of swallowing and speech. It also obviates the need for a prosthesis which can be uncomfortable particularly in those patients who require radiation (Fig. 12.6).

Finally, patient’s recurrent disease following radiation therapy may be not appropriate candidates for TORS. Some studies have made specific exclusion criteria to include invasion of the mandible, involvement of greater than half of the posterior pharyngeal wall and/or tongue base, unresectable neck nodes, prevertebral fascia fixation, and carotid artery involvement (the latter two factors representing stage IVB disease), though this is a matter of debate depending on the situation.

12.6 Operative Margins

It is important to note that there is some disagreement with what constitutes negative margins in TORS. In this light, some studies have suggested that negative margin is defined by at least 1 cm of normal mucosa tissue, while some other studies have described closed, yet negative, margins as meaning 2 mm of normal tissue. An analysis of several studies and what the researchers defined as “close” or “negative” margins suggest some variability in the literature, though most studies agreed with 2-mm margins as close and 1-cm margins as constituting negative margins although significant variation exists in the literature. The “appropriate” surgical margin may also vary depending on anatomical subsite, an example being the difference in adequate tonsil margins (often adjacent to parapharyngeal space) and base of tongue margins which may have different distances despite clearance of disease. Tumors that affect the tonsil provide the pharyngeal constructors as a deep margin. Anatomically, this area will only provide for between 1 and 3 mm. The cross-sectional anatomy (Fig. 12.1) demonstrates the thin layer of constrictor muscle separating the tonsil from the parapharyngeal space. Additionally, the mucosa often shrinks following surgical excision leading to misleading mucosal margins (Fig. 12.7). In contrast, the tongue base resection allows for a 1-cm margin and can more accurately be assessed. Communication with the pathologist is important to ensure that there is no misunderstanding related to the unique circumstances associated with transoral resection.

Note

There is no consensus on what constitutes a “negative margin,” however, it is clear that a positive margin is a poor prognosticator. Whether the margin is 1 or 3 mm, a negative margin is critical.

12.7 Surgical Morbidity

The morbidity of the traditional open surgical approach can be significant when compared to transoral approaches and is likely the reason behind the rise in nonsurgical therapy in this disease. Advanced-staged tumors of the tonsillar fossa generally require a longer, more complicated surgery when a traditional open approach is employed. In some cases, access to the lateral oropharyngeal wall can require a lip-splitting procedure in
conjunction with a mandibulotomy. These open cases often require a tracheostomy and generally require an alternate means of feeding, sometimes permanently, if the dysphagia is severe and long term. Certainly access to the base of tongue is enhanced during TORS and surgical morbidity is decreased when compared to mandibulotomy or transcervical pharyngotomy. Relating to the base of tongue, open surgical management, similarly to open resection of tonsillar fossa tumors, can be associated with increased morbidity. Indeed, an open approach to the base of tongue can achieve excellent local control, but this often comes at the price of increased morbidity.

The transoral approach to the tonsillar fossa has particular advantages over traditional open approaches although traditional transoral radical tonsillectomy continues to be a viable option for many patients. A study by Weinstein et al of 27 patients undergoing a radical tonsillectomy found that only two patients required a tracheostomy at the end of the procedure or in the perioperative period. Further studies have mirrored this finding. Furthermore, the authors reported that 26 of 27 patients were able to swallow without the need for a feeding tube at the conclusion of the study.71

Several studies have shown that TORS can decrease morbidity while achieving comparable locoregional control as compared to more traditional open approaches in appropriately selected cases. Mercante et al reported that 92% of patients with T1 or T2 base of tongue SCC had negative margins, though this study only included a limited number patients. In this study, tracheostomy was required for a mean of 6 days and nasogastric tube was required for a mean of 7.5 days,72 although in general tracheostomy is quite rare in this patient population in our experience. Similarly, Moore et al showed that 54% of patients undergoing TORS at their hospital required tracheostomy in more advanced disease. In patients with T3 and T4 disease, Moore et al found that 27% required a percutaneous endoscopic gastrostomy tube and that at 4 weeks’ postoperatively, 90% of the patients included in the study were tolerating an oral diet.73 Moreover, the literature suggests that the rate of positive margins with TORS is comparable to traditional transoral techniques, with Moore and colleagues noting 6.2% rate of positive margins compared with 3.9% with the more traditional approach.10

Related to recurrence, TORS has been reported to be comparable if not superior to an open approach for salvage surgery, although the impact of surgical selection bias is obvious in this data. The argument that patients in need of salvage surgery are poor candidates for transoral surgery is a matter of continued debate. In fact, some authors argue that TORS may be performed in a salvage setting for certain patients. One study concluded that TORS in salvage OP cases compared to open salvage cases was associated with shorter operative time, less blood loss, shorter hospital stay, lower postoperative complications, and “acceptable” 2-year survival rates.74 Furthermore, patients who underwent a TORS procedure for recurrence rated better quality of life in certain aspects of their life, including speech and swallowing function.75 Patients undergoing robotic-assisted salvage surgery, due to the minimally invasive nature of the procedure, have lower rates of certain complications when compared to open approaches that have been associated with bone exposure, mandibular malunion, reconstruction-related complications, and the need for hardware removal secondary to infection.76

12.8 Neck Disease

Addressing the cervical lymphatics when treating oropharyngeal malignancy is widely accepted in the literature. While traditionally treated with radiotherapy or concurrent chemoradiotherapy, in the setting of TORS the treatment of the neck is generally selective neck dissection. The extent of the neck dissection is
related to the anatomical location of the disease, the extent of disease, and the preoperative cervical staging. Details related to the technical aspects of neck dissection are beyond the scope of this chapter; however, some mention of the sequencing of neck dissection is warranted. Some centers advocate staged neck dissection, with the neck dissections being performed in a subsequent surgical procedure after a designated period of healing after completion of TORS.\(^{71,77}\) Other centers advocate concomitant neck dissection at the time of the TORS procedure.\(^{78,79}\) Advantages to the staged neck dissection include the prospect of decreased cervical fistula rates, decreased operative time, and improved robotic resources utilization, while advantages of concomitant neck dissection include a single operative intervention, ability to control cervical vessels (i.e., lingual artery ligation) at the time of TORS, avoiding delay in adjuvant therapy, and decreased total operating room costs.\(^{80}\) Certainly the sequencing of neck dissection varies from center to center, however, the majority of centers prefer concomitant neck dissection.

### Note

The sequencing of neck dissection varies from center to center, however, the majority of centers prefer concomitant neck dissection.

#### 12.9 Adjuvant Therapy

A more detailed discussion of adjuvant radiation and chemotherapy is included in other chapters in this text. In relation to TORS, we will discuss briefly the indications for postoperative irradiation as well as chemotherapy. This chapter will mostly focus on the current paradigm of therapy and the concept of de-escalation trials.

Presently, many centers continue to follow traditional guidelines in the application of adjuvant radiation and chemotherapy after transoral surgery. Most centers agree that adverse features such as perineural invasion, lymphovascular invasion, or multiple cervical lymph node metastasis (especially matted nodes) warrant adjuvant radiation. Similarly, extracapsular extension or positive margins also warrant the addition of chemotherapy in many institutions. Advanced-stage endophytic T3 and T4 tumors should also receive postoperative adjuvant therapy, but one can make the argument that TORS may not provide a significant benefit in this patient population. That being said, there is some evidence that transoral surgery has the potential to improve oncologic outcomes for advanced-stage lesions.\(^{81}\)

However, the application of adjuvant therapy after TORS is currently undergoing an examination by investigators around the world. Significant controversy exists regarding the current staging system, the appropriate dosage of radiation, and the application of chemoradiation after TORS for HPV-related OPSCC.\(^{87}\) Large randomized controlled trials have shown that the 3-year locoregional rate of control of patients who have HPV-positive disease that undergo adjuvant multimodality therapy is 85% compared to 65% in patients who are HPV negative. The authors argue that being HPV positive and receiving adjuvant chemoradiation reduces the risk of death from the OPSCC by 60%.\(^{26}\) However, the functional results of these trials have been less than optimal, and certainly the question currently being evaluated is whether transoral techniques can provide similar oncologic outcomes with improved functional results. Preliminary data indicate that this is in fact the case, however, several large trials are currently being conducted to answer this question.

These so called “de-escalation trials” fall into one of the following categories: de-escalation involving surgery, de-escalation by replacing cisplatin with cetuximab in order to decrease the toxicity profile of treatment, and de-escalation trials determining if induction chemotherapy followed by decreased radiotherapy dose is appropriate in good responders, or radiation dose reduction strategies. A variety of other options including decreased radiation dosage, altered fractionation schemes, decreased chemotherapy dosage, or altered administration strategies are being evaluated around the world. The Eastern Cooperative Oncology Group E3311 (ECOG E3311) trial compares patients with p16-positive oropharyngeal cancer who have upfront transoral surgery in a randomized nature to see if surgery can reduce the dose of radiation from 60 to 50 Gy. Patients included from multiple institutions who had intermediate-risk features associated with stage III or IV OPSCC defined as having close margins (defined as <3 mm), extracapsular extension outside any of the lymph nodes surgically removed, and two to four metastatic lymph nodes on neck dissection. The three treatment arms include observation, postoperative radiation (50 Gy), postoperative radiation (60 Gy), and cisplatin with radiation in high-risk patients defined as those with positive margins or extracapsular spread (>1 mm). This study is important for establishing de-escalation is based on the principle that a decrease in the radiation dose to the head and neck has an associated decrease in long-term morbidity and improved functional outcomes, including decreased osteoradionecrosis, pain, scarring, dysphagia, xerostomia, carotid stenosis, and gastric tube dependence. The primary end point of the study is 2-year disease-free survival in patients with stage III or IV tumors that can be resected surgically via a transoral approach. As of April 2015, in the 135 patients included in the study, de-escalation (the 50-Gy group) has demonstrated “safety and feasibility” with regard to postoperative bleeding risk, surgical quality, and positive margins.\(^{82}\)

The Sinai Robotic Surgery Trial in HPV-Positive Oropharyngeal Squamous Cell Carcinoma (SIRS) trial looks at patients with HPV-positive oropharyngeal cancer who have undergone TORS and are assigned to low-risk (observation), intermediate-risk, and high-risk adjuvant therapy strategies based on pathologic data from surgery. The study will also examine treatment failures and salvage therapy in this patient population. The trial has relatively aggressive dose reduction for radiation in this setting and will determine if patients undergoing TORS can be spared radiation therapy postoperatively or undergo significant dose reduction in adjuvant radiation if favorable pathologic features are present.\(^{83}\)

The Adjuvant De-escalation, Extracapsular Spread, p16-positive, Transoral (ADEPT) trial was designed for OP malignancy. Patients in this study have p16-positive OPSCC who have had all known disease removed surgically via transoral surgery. The patients must have extracapsular spread pathologically in the lymph nodes removed during neck dissection. The patients can either be randomly assigned or have the potential to choose postoperative radiation or concurrent chemoradiotherapy. The
patients will receive intensity-modulated radiation therapy (IMRT) at 60 Gy alone or IMRT with cisplatin.84

The UK-based PATHOS trial, currently in phase II, looks at patients with OPSCC that are HPV positive and are T1 to T3 and N1 to N2b. All patients will receive transoral surgery with concomitant ipsilateral neck dissection. Patients who, pathologically, have intermediate-risk or high-risk features are randomized within their risk group to receiving low dose compared to standard-dose IMRT or to receive standard dose IMRT compared with cisplatin and standard-dose IMRT.85

Several studies are currently looking into replacing cisplatin with cetuximab with radiation therapy. The Radiation Therapy Oncology Group (RTOG-1016) multicenter trial which is looking into patients with p16-positive OPSCC that is stages III and IV and randomizing patients to cetuximab with radiation (70–72 Gy) as opposed to cisplatin with radiation (70–72 Gy). Both groups will get accelerated IMRT. The primary outcome of the study is 5-year overall survival. Currently, the trial is in phase III with the working hypothesis that cetuximab and external beam radiation therapy (XRT) will have less morbidity without compromising overall survival.86 Similarly, the Trans-Tasman Radiation Oncology Group (TROG)87 and De-ESCALaTE trials88 (in the United States and United Kingdom, respectively) consist of p16-positive OPSCC and randomizing patients into cetuximab or cisplatin with conventional fractionated IMRT. These trials are also in phase III and results should be available in the near future.

Other studies are looking into induction chemotherapy followed by decreased radiotherapy in “good responders.” The Quarterback trial is evaluating patients with HPV-positive OPSCC and patients who respond well to induction chemotherapy with carboplatin are randomized into either a group with a reduced XRT dose (56 Gy) or standard dose (70 Gy). The study is still accruing at the time of the writing of this chapter.89 ECOG 1308 is a multicenter study looking at patients diagnosed with stage III or IV HPV-positive OPSCC and patients will undergo induction chemotherapy before randomization to IMRT groups (54 or 70 Gy) concurrently receiving cetuximab. Unlike some other de-escalation trials, ECOG 1308 has some preliminary data suggesting that the group of patients who respond to induction chemotherapy may have lower 1 year failure rates even with a reduced dose of radiation.90

The results of these and other de-escalation trials should guide the design of further research in the field, and provide data to alter treatment strategies in the HPV-positive patient population, with the goal to maximize oncologic control while maintaining acceptable functional outcomes.

12.10 Conclusion

HPV-related OPSCC is on the rise. Data regarding oropharyngeal cancer have historically been obtained in the pre-HPV era. As a result, a frameshift is currently under way regarding the way in which physicians and surgeons look at oropharyngeal cancer. The current understanding and pathogenesis of HPV and the pattern of the disease remain under active investigation. Even with the current increase in research related to HPV-positive OPSCC, the mechanisms of the disease remain largely unknown. Minimally invasive transoral approaches to the oropharynx, particularly TORS, offers several technical and functional advantages over traditional open approaches. Given the recent advent and recent advances in TORS, surgeons continue to evaluate TORS for OPSCC, particularly early-stage HPV-positive SCC. Also of great excitement are the plethora of “de-escalation” trials that are emerging. These “de-escalation” trials have the potential to provide significant useful information in the management of OPSCC in the future.

12.11 Clinical Cases

12.11.1 Case 1

History

A 59-year-old man presented with a right tonsil mass found on routine physical examination. The asymmetry of the tonsils prompted a biopsy performed in the office. Patient reported throat pain but no significant dysphagia. The patient denied weight loss, shortness of breath, hoarseness, or hemoptysis. The biopsy was consistent with SCC. The biopsy was evaluated for HPV by p16 staining and polymerase chain reaction (PCR) analysis, both were positive. The tumor virus was also typed HPV35.

The past medical history was significant for hepatitis C, hypertension (HTN), and diverticulitis. The patient was taking hydrochlorothiazide. The patient's social history was significant for a half-day pack per day of cigarette use for 30 years and a history of heavy alcohol use (quit 10 years ago).

Physical Examination and Imaging

On physical examination, the oral cavity and oropharynx revealed an enlarged right tonsil that was slightly firm on palpation. The neck examination demonstrated multiple palpable right-sided cervical lymph nodes in levels II and III but no palpable lymphadenopathy on the left side of the neck was noted. The fiberoptic examination demonstrated that the larynx was normal and the true vocal cord motion was. The pyriform sinuses were clear. A positron emission tomography (PET)/CT scan of the neck with contrast was ordered. There was asymmetric nodular soft tissue at the lateral tonsillar fossa extending into the right glosstonsillar sulcus. There was a right level 2A and 2B necrotic/cystic metastatic adenopathy. The PET demonstrated increased 18F-fluorodeoxyglucose (FDG) uptake at the right tonsillar region (standardized uptake value [SUV] max 15.4). There was increased metabolic activity along the right anterior vocal fold (SUV max 7.1) with no abnormal CT correlate. There was FDG-avid right level 2A/2B cervical lymph nodes. Subcentimeter FDG-avid right levels III and V lymph nodes were detected. A fine-needle biopsy of the left and right
The biopsy was evaluated for HPV by p16 staining and PCR the right neck mass and the biopsy was consistent with SCC. The physical examination revealed a 2.3-cm right level II hypermetabolic lymph node with no obvious primary source.

**Options for Management**

The workup of the unknown primary has changed as HPV-associated disease has become more common. The traditional approach to a primary of unknown origin has been a diagnostic laryngoscopy, directed biopsies, and tonsillectomy under general anesthesia. However, an alternative approach focusing on the palatine and lingual tonsils has gained popularity as HPV-associated disease has become more prevalent. In this approach, a lingual tonsillectomy is performed as part of the directed biopsies. This can be achieved through the transoral approach.

The rationale for this approach is the well-documented subcentimeter primary carcinomas that have been routinely found deep within the crypts of the lingual tonsils. Because these cancers may not be clearly identifiable and because they may originate within the tonsillar crypts, a lingual tonsillectomy may be the most reliable approach to identify the primary cancer.

**References**


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Transoral Robotic Management of the Oropharynx

13 Reconstruction of the Oropharynx

Tamer A. Ghanem and Zaahir Turfe

13.1 Introduction

The oropharynx plays a crucial role in swallowing, speech, and respiration. Successful reconstructive surgery of the oropharynx must accommodate these functions. To understand oropharyngeal reconstruction, it is essential to understand the different surgical approaches to achieve ablation of oropharyngeal carcinoma. The two primary ablative approaches are transmandibular (lip and mandible splitting), and lateral pharyngotomy approach (cervical access to the lateral oropharynx). These surgical procedures involve considerable morbidity including the need for a tracheostomy, long-term feeding tube, impaired speech, and/or an increased hospital length of stay. Nevertheless, these approaches are still widely used, especially in the salvage surgery.

Transoral robotic surgery (TORS) is relatively new surgical approach that is commonly used for the management of early-stage oropharyngeal cancer. In the case of TORS, the wound bed is commonly allowed to heal by secondary intention. Studies have found that TORS is associated with a decreased need for tube feeding, improved functional outcomes, and faster recovery when compared to open approaches. However, the management of larger cancers often involves an extensive dissection and exposure of the great vessels. In contrast to the TORS defect, these defects are typically more extensive. As a result, a reliable reconstruction is critical to separate vascular structures of the neck from the oral cavity. This is particularly important in the salvage setting where wound healing is often compromised and a pharyngocutaneous fistula can lead to devastating consequences such as the vascular rupture.

Reconstruction of the oropharyngeal defect has undergone an evolution over the past 30 years. Prior to the introduction of free tissue transfer in the 1980s, regional flaps represented the traditional approach to head and neck reconstruction. The pectoralis myocutaneous (PMC) flap was a common choice because of its reliable blood supply and well-vascularized muscle (**Fig. 13.1**). The advent of microsurgery permitted surgeons the ability to tailor a free flap to best accommodate the head and neck defect. Free tissue transfer also provided variety of different types of tissue including muscle-containing flaps, thin pliable flaps, bone-containing flaps, and enteric flaps. The thin, pliable vascularized skin paddle associated with the radial forearm free flap (RFFF) is a common choice for oropharyngeal reconstruction because of the ability to recapitulate the contour of the complex oropharyngeal anatomy. Subsequently, a variety of options including the anterolateral thigh free flap (ALTFF) have been introduced for complex reconstruction of the oropharynx. These flaps provide excellent options for oropharyngeal reconstruction, however, the complexity of this task cannot be underestimated.

Although many chapters focus on the type of tissue that apply to oropharyngeal reconstruction, there is a paucity of literature dedicated to the actual process of designing the flap to achieve the optimal reconstruction. This is an important consideration because if the flap is not appropriately designed, excessive bulk can lead to dysphagia and airway obstruction.  

The paucity of the literature related to this issue reflects the difficult task of articulating flap design. Estimating the size of the flap and taking into consideration that the tissue must accommodate replating a mandibulotomy is a tall order for a written text. Often, the finer points of flap reconstruction are best learned by observing an experienced reconstructive surgeon. The advent of TORS brings with it a shift in the field and a shift in the approach to oropharyngeal reconstruction. Although the open approach remains a popular surgical approach, transoral robotic reconstructive surgery (TORRS) for oropharyngeal defects is gaining popularity. Ultimately, the choice of reconstruction, and whether reconstruction is necessary, depends on resection approach, patient factors, extent of the defect, and whether surgery is performed in the primary or salvage setting.

Finally, when evaluating an oropharyngeal defect and in determining the most appropriate reconstructive approach, the goals of reconstruction must be kept in mind (**Table 13.1**). These goals not only include reestablishing the soft tissue defect and protecting the great vessels, but functional reconstruction such as maintaining velopharyngeal competence and mobility of the base of tongue are critically important to the pharyngeal...
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Table 13.1 The goals of oropharyngeal reconstruction
- Protect the great vessels
- Maintain velopharyngeal competence
- Prevent tethering of the base of tongue
- Maintain the bulk necessary to achieve tongue and palatal contact

One of the most important considerations when managing a defect of the oropharynx is the soft palatal defect. Defects that

functions to provide sensation of the mucosal membranes of the pharynx, palatine tonsil, soft palate, tonsillar pillars, and posterior third of the tongue. It also provides motor innervation to the stylopharyngeus, and the pharyngeal constrictors.7,8

13.3 Evaluation of the Oropharynx Defect and Determining Options for Reconstruction

13.3.1 Evaluation of the Defects

Defects of the oropharynx are characterized based on the size, location, and presence of complicating factors. The size of the defect is important to assess because it may help determine the optimal donor site. Large defects may require a donor site such as at the ALT which has the potential to provide a large skin paddle. In contrast, the RFFF donor site may not provide enough skin to appropriately cover an extensive defect. The location of the defect is similarly important. In complex defects of the oral pharynx that require delicate tailoring up the flap, the radial forearm free flat may provide pliable tissue that accommodates the complex undulating anatomy. In contrast, the ALT flap may provide too much bulk for a defect of this nature and lead to airway obstruction or dysphasia. A thoughtful approach to the reconstruction and an intimate understanding of speech and swallowing mechanisms are helpful as the surgeon decides on his/her reconstructive choice.9

The oropharynx plays an important role in the oropharyngeal phase of deglutition. Its role in swallowing includes the initiation of swallowing as the soft palate is drawn forward, while the tongue base elevates during the oral preparatory and oral phases of swallowing. This integrated movement prevents food from spilling into the larynx. Surgical compromise of the soft palate and/or base of tongue will increase the risk for aspiration. As the oral phase of swallowing is completed, the food bolus is pushed posterior between the tongue and palate resulting in the initiation of the pharyngeal phase of swallowing. This phase concludes with the transit of food into the esophagus via velopharyngeal closure, elevation and closure of the larynx, contraction of the pharyngeal muscles, and retraction of the base of tongue. The base of tongue transmits the major force and pressure responsible for the transit of the food bolus through the pharyngeal phase. With regard to speech, ablation of more than 50% of the soft palate often results in velopharyngeal insufficiency and long-term speech impairment. Additionally, ablative surgery can result in dysphagia and aspiration secondary to pharyngeal stenosis, malfunction of the base of tongue as a result tethering or decreased base of tongue volume, or sensory denervation.10

In evaluating the oropharyngeal defect for reconstruction, each of the functional elements, speech, swallowing, velopharyngeal closure, and airway protection should be carefully considered as the donor site is contemplated and the design of the flap it is considered. While regional and free tissue transfer flaps do not provide functional elements such as muscular contraction and movement, reconstitution of the natural anatomical contour will ultimately help preserve function.

One of the most important considerations when managing a defect of the oropharynx is the soft palatal defect. Defects that
involve 50% or greater of the soft palate should be managed with soft tissue reconstruction. While prosthetic management can be achieved, generally the functional results are suboptimal and patients commonly complain of pain and irritation. This is most problematic in patients who have been treated with radiation therapy. Soft tissue reconstruction can be managed by closing the pharyngeal mucosa to the free edge of the soft palate (▶ Fig. 13.2). A soft tissue flap can then be placed over the velopharyngeal reconstruction to aid in healing and provide soft tissue reconstruction of the lateral pharyngeal wall.

13.3.2 Determining Reconstructive Options

Choosing the best donor site requires a careful consideration of the patient’s medical status and limiting factors in the patient’s occupational and recreational interests. A thorough assessment of the patient’s overall medical condition is important. Comorbidities that adversely impact wound healing such as arterial disease, diabetes, steroid use, previous radiation, and nutritional deficiency must all be taken into account. Other comorbidities such as coronary artery disease, chronic obstructive pulmonary disease, and poor functional status may preclude a prolonged surgical procedure and should encourage the surgeon to seek a simple, expedient, and effective reconstructive option. Additional considerations include the patient’s occupational and recreational interests. If the patient utilizes his/her hands for work or recreation, then the patient may not be an ideal candidate for RFFF given the potential limitations on range of motion and hand strength. In contrast, the patient with the
Reconstruction of the Oropharynx

preexisting lower extremity deformity may not be best suited for an ALTF.

**Note**
When determining the reconstructive options, a careful medical history in addition to a social and occupational history is an important part of the decision process.

After evaluating these factors, a comprehensive analysis of the defect should be completed. The size of the defect and the involvement of soft tissue and bone must be noted. The dimensions of the defect can be measured in all its parameters using a ruler or a template of the defect can be constructed.

Perhaps, most importantly, the surgeon must keep in mind the ultimate goal of the reconstruction of the oropharynx: to provide each patient with the highest possible quality of life via the restoration of speech, permit an oral diet, and establish a stable airway without the need for a tracheostomy. A more detailed explanation of determining the best reconstructive approach is explained in the upcoming section.11

### 13.4 Classification of Oropharynx Defects

The classification of oropharyngeal robotic defects (CORD) provides a reconstructive framework for defects (see Chapter 8, Figs. 8.3–8.6). CORD is based on two important criteria: (1) number of subsites involved; and (2) presence of an adverse feature, such as exposure of internal carotid artery, communication with oropharynx, and whether more than 50% of soft palate has been resected.

Briefly, class I defects involve only one subsite and have no adverse features. Class II defects involve more than one subsite and have no adverse features. Class III defects involve one subsite and also have at least one adverse feature. Finally, class IV defects involve more than one subsite with at least one adverse feature.

The specific reconstructive donor site cannot be dictated by an algorithm as each defect is unique in its proportions and coexisting pathology, however, the CORD classification provides a framework to guide oropharyngeal reconstruction. Classes I and II defects typically can be managed with secondary healing, primary closure, or local flaps. Small defects such as those created by the resection of a T1–T2 tonsillar cancer with no neck communication can be left to heal by secondary healing. A small palatal defect can be treated by tacking the remaining soft palate to the nasopharynx to avoid velopharyngeal insufficiency. Regarding the tongue base, defects less than 50% of size can typically heal secondarily. The reconstructive surgeon should be aware that primary closure should not be performed on patients on steroids, radiated necks, bone exposure/neck fistulas, or poor nutritional status. These defects are best addressed with vascularized tissue such as local or free tissue transfer.

Classes III and IV defects typically require either a regional flap or a free flap. Moderate-sized defects are those that involve greater than 50% of the base of tongue, a resection of a large portion of the soft palate or a pharyngectomy. These defects can be reconstructed using a regional flap such as the pectoralis major flap. The pectoralis major flap is associated with excess bulk and may lead to impaired speech and swallowing. Other regional flaps include the lower trapezius flap and pedicled latissimus dorsi flap. We prefer to utilize a free microvascular free flap in these instances. Similarly, larger defects can be closed with a pedicled flap (pectoralis major, latissimus dorsi). The disadvantage of pedicled flaps and myocutaneous flaps is that the muscle atrophies make it difficult to predict the final soft tissue volume and bulk. Additionally, pedicled flaps can suffer from gravitational pull which can distort the anatomy and impair function. Thus, we prefer free tissue transfer, mainly RFFF for these cases.12

The RFFF can be used to reconstruct total palatal, tonsillar, base of tongue, and hypopharyngeal defects. In our experience, free flaps offer improved sensation and swallowing. Other free flaps that can be used include the lateral arm, the rectus abdominus, the jejunum, and the gastro-omentum flap.

**Note**
The CORD classification system provides a guideline for oropharyngeal reconstruction, but choosing the appropriate donor site requires a critical assessment of the defect and the options for donor tissue.

In the following section, we present the various reconstructive options for oropharyngeal reconstruction. This section is organized according to the reconstructive ladder. We describe the surgical approach to skin grafts, local flaps, regional flaps, and free flaps with an emphasis on the most appropriate flaps for reconstruction of the oropharynx selected by category.

### 13.5 Split-Thickness Skin Graft

#### 13.5.1 Patient Selection

Skin grafts can be used to close small defects of the lateral pharynx, posterior pharynx, and tonsillar region that cannot be closed in a primary fashion. In selecting a good candidate for a skin graft, consideration must be given to the size of the defect as well as the vascularity of the underlying tissue. Healthy non-radiated muscle in the underlying wound bed will support a skin graft and improve healing. Consideration must also be given to the donor-site morbidity. A split-thickness skin graft (STSG) is typically taken from an unexposed body site such as the upper thigh. The donor site can be painful but generally heals without a significant risk of complications.

#### 13.5.2 Surgical Technique and Considerations

A split-thickness graft consists of the epidermal layer and a portion of the underlying dermis. The graft can be harvested using a dermatome to harvest a thin graft (<0.01 inches). The tools to harvest the graft include a manual dermatome as well as a powered dermatome. We prefer to use a powered dermatome to ensure uniformity of the graft in thickness. The dimensions of the graft should be 15 to 20% larger than the area of defect. The donor site is lubricated and the area is kept as flat as
possible during the harvesting procedure to ensure uniform thickness. A surgical assistant should apply counter tension while harvesting the graft. The graft should be sutured in place to reconstruct the geometrical defect. Underlying serous or bloody discharge can increase the risk of graft failure and may be a source of infection, thus small incisions can be made into the graft to prevent the accumulation of fluid or blood beneath the graft. Care to maintain immobilization of the reconstructive region using a bolster dressing can minimize tension on the graft and improve healing. Sutures placed to tact down the skin graft to the wound bed will also help graft viability. An epinephrine-soaked sponge can be applied to the donor site to reduce bleeding and a layer of xeroform gauze can be applied to the donor site and left in place. Alternatively, fibrin glue can be placed on the skin graft donor site and a large clear plastic dressing can be placed over the wound. This reconstructive option is straightforward but requires appropriate patient selection.

13.5.3 Perioperative Management

The donor site will typically heal over the course of 7 to 14 days. Artificial or biological dressings can be applied over the donor site to promote healing. Relevant complications include graft contraction and graft failure and sloughing. Secondary contraction of the graft is usually a result of scarification of the dermal component of the graft. This can be avoided by using thin grafts and ensuring redundancy of the graft over the defect. Primary contracture of the graft is the elastic recoil of the skin that occurs as soon as the graft is harvested. A STSG of medium thickness will contract by approximately 20%, and a thin STSG will contract less, approximately 10%. Immobilization assists greatly in preventing contraction. Common causes of graft failure include inadequate blood supply, underlying hematomas or seromas, graft shearing or inadequate postoperative immobilization, infection, technical errors, and/or inadequate patient nutritional status.

13.5.4 Pearls

Choose the inner aspect of the thigh as the donor site for the split thickness as it conceals the donor site nicely compared to the lateral side.

Note

Successful healing of a split thickness requires a wellvascularize wound bed. As a result, patients who have been previously treated with external beam radiotherapy are not good candidates for skin graft reconstruction.

13.6 Facial Artery Musculomucosal Flap

13.6.1 Patient Selection

The facial artery musculomucosal (FAMM) flap is a pedicled local flap that is associated with minimal harvest site morbidity; it is technically straightforward to harvest, and the FAMM flap is not confounded by patient morbidities such as diabetes, hypertension, and poor wound healing. This flap was originally described by Pribaz in 1992. It is an intraoral axial patterned flap. The blood supply for this flap is the facial artery. This flap is ideally used for reconstruction of the medium-sized defects of the soft palate. Contraindications include prior neck dissection with facial artery sacrifice, history of radiation, and a lack of Doppler signal along the path of the facial artery (this is an absolute contraindication).

13.6.2 Surgical Technique and Consideration

The most important preoperative step is to ensure a fully functional facial artery via Doppler signal availability. This step is especially crucial in patients who have undergone ipsilateral neck dissection or previous radiation treatment to the head and neck region. The facial artery and the FAMM arterial branches travel over the inferior border of the mandible. At the level of the oral commissure, approximately 15 mm lateral to the commissure, the facial artery contributes three to five branches to the buccinator muscle and the overlying buccal mucosa before it terminates. It runs deep to the risorius and the zygomaticus and superficial to the buccinator, levator anguli oris, and orbicularis oris.

In preparation for surgery, the patient is nasotracheally intubated, the facial artery is traced, and Doppler is used introrally to track the path of the vessels along the gingivobuccal sulcus. The flap can be inferiorly based of superiorly based. An inferiorly based flap is harvested by making an incision either at the distal aspect of the planned flap or at the oral commissure. Dissection is then completed through the buccinator muscle to find the facial artery. The facial artery is ligated at the distal aspect of the flap; dissection of the flap is completed distal to proximal with care to include buccinator fibers to protect the facial artery. The flap can be designed no more than 2 to 3 cm to prevent injury to Stenson’s duct. Once the flap is elevated, a trough is made from the proximal superior incision at the flap base laterally to connect the flap to the defect (Fig. 13.3). The flap is then rotated to the defect or through a submucosal tunnel. The surgeon should take care to prevent twisting the pedicle which could disrupt the facial artery blood supply. The Doppler can be used to ensure the integrity of facial artery blood supply. The donor site is closed in a two-layer fashion—muscle and then mucosa.

The superiorly based flap relies on the retrograde flow from the angular artery. In this surgical approach, the flap is harvested from the distal end (near the retromolar area) deep to the facial artery. The flap is fully mobilized and then transferred to the area of defect.

13.6.3 Perioperative Management

Potential complications to be aware of include partial or total flap necrosis. There is also a risk for dehiscence, hematoma formation, and infection.
Note
The FAMM flap depends on an intact facial arterial system. An arterial Doppler can be performed while planning the flap to ensure vascular integrity. This especially important in patients who have undergone a prior neck dissection.

13.7 Pectoralis Major Flap

13.7.1 Patient Selection

The pectoralis myocutaneous (PMC) flap is a myocutaneous flap that is nourished by the pectoral branch of the thoracoacromial artery. This is an exceptionally reliable donor site that has few contraindications. In considering patient selection, patients with a high body mass index (BMI) or patients who are excessively muscular may yield an exceptionally thick flap that can complicate oropharyngeal reconstruction because of excessive bulk.

13.7.2 Surgical Technique and Consideration

The PMC flap is commonly used in head and neck surgery. The dominant pedicle is the pectoral branch of the thoracoacromial artery and vein which are branches of the axillary vessels. The pedicle can be reliably located on the undersurface of the pectoralis muscle approximately halfway between the sternal notch and deltopectoral groove. The flap design should be outlined with a marking pen (Fig. 13.4). Key landmarks should
be marked out including the clavicle, xiphoid, and ipsilateral sternal border. The initial incision is made at the lateral part of the pectoralis major; the inferior, medial, and lateral incisions are made through the skin and subcutaneous tissue. The incision should be carried down through the pectoralis fascia down to the chest wall (▶ Fig. 13.5). The superior incision is then completed through the muscle fibers and the skin island is sutured to the pectoralis muscle with absorbable sutures. This helps to protect the skin paddle myocutaneous perforators. The muscle is elevated from inferior to superior, and the pedicle is identified and protected. Care must be taken to avoid cutting the internal mammary perforators when dissecting the muscle fibers along the sternal attachment. The distal end of the skin panel can be used to achieve the reconstruction. The flap can be designed in a way that the deltopectoral flap is preserved in the event that it is needed in the future (▶ Fig. 13.6). In the case that the distal aspect of the flap is too bulky, the surgeon can narrow the pedicle. Once the flap is dissected off the chest wall, a subcutaneous tunnel is formed and the flap is tunneled to the recipient site (▶ Fig. 13.7). In the case of a bulky flap, lubrication can be used and the ipsilateral shoulder can be raised to facilitate transfer of the tissue to the neck through the subcutaneous tunnel. If desirable, the skin can be removed from the flap and underlying fat can be resected to debulk the flap resulting in a thinner flap. If additional length is needed, the skin paddle can be extended as a random pattern flap beyond the inferior edge of muscle belly. Another option is to divide the clavicular portion of the pectoralis major muscle by debulking the muscle fibers over the proximal pedicle. One of the major disadvantages of this donor site is that the bulk of this donor site can obstruct the airway. Similarly, the excessive bulk can pull on the flap resulting in a dehiscence and wound breakdown. In contrast, the muscle may be used to protect the great vessels (▶ Fig. 13.8).
13.7.3 Perioperative Management
Postoperatively, it is important not to place pressure on the vascular pedicle as it crosses the clavicle. As a result, compression dressings in this area are contraindicated.

13.7.4 Pearls
The pectoralis major is a robust flap except those who are cachectic. In addressing defects of the oropharynx, the muscle-skin paddle composite can often be too bulky and a muscle-only flap can be used.

Note
While the PMC flap provides an excellent source of vascularized muscle and a reliable skin paddle, patient selection is essential. A bulky flap can adversely affect speech, swallowing, and the patient’s airway. A muscle-only flap cannot provide a remedy for this shortcoming.

13.8 Radial Forearm Free Flap
13.8.1 Patient Selection
This is a popular flap due to reliable vascular anatomy, ease of dissection, long pedicle, and thin, pliable skin paddle. The arterial blood supply to this flap is the radial artery, and the venous drainage is via the venae comitantes. The cephalic vein can be harvested with the flap to give an additional venous outflow especially if the caliber of the venae comitantes is too small. The skin paddle has numerous perforators from the radial artery and thus allows for the flap to comply with the complex three-dimensional geometry of the oropharynx.

13.8.2 Surgical Technique and Considerations
The nondominant hand is chosen for the surgery. Venous access restricted to the non-donor arm. A preoperative Allen’s test is performed. The RFFF is a fasciocutaneous flap. Therefore, this donor site provides thin pliable tissue that is amenable to the
than half the base of tongue, exposure of the carotid artery, and/or involvement of more than half the base of tongue. The current approach following TORS oropharyngeal resections is to permit healing by secondary intention. The disadvantages of this donor site include the high rate of donor site complications.

Table 13.2

<table>
<thead>
<tr>
<th>Indications for transoral robotic free flap reconstruction</th>
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<tbody>
<tr>
<td>Large defects (T3, T4)</td>
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<tr>
<td>Resection of more than half the base of tongue</td>
</tr>
<tr>
<td>Exposure of the carotid artery</td>
</tr>
<tr>
<td>Resection of the soft palate</td>
</tr>
<tr>
<td>Salvage surgery</td>
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</table>

In choosing the appropriate patient for this technique, it is essential that the robotic instrumentation can be placed intraorally. Trismus, limited neck extension, macroglossia, and obesity may hinder robotic access limiting the ability to achieve transoral robotic flap reconstruction. For these patients, transmandibular approach with lip splitting is often necessary.

13.9.2 Surgical Technique

The flap of choice is harvested as mentioned previously. The robotic unit is docked at 30 degrees to the base of the bed. The da Vinci robot is positioned contralateral to the side of flap harvest. It is placed at approximately 30 degrees from the patient with the 30-degree endoscope (allows improved visualization in the base of tongue and inferior oropharynx) and a 5-mm needle driver is used in both arms. The primary surgeon operates from the console according to standard robotic surgery setup. An assistant is positioned at the patient’s head to help with introducing the suture to the surgical field, cutting suture, and providing retraction of surrounding tissue.

The flap pedicle is passed transorally using a 1-inch Penrose drain from the mouth into the ipsilateral neck. The skin paddle is positioned in place to fit the defect. At this stage, any excess skin paddle can be trimmed. The skin paddle is secured with two sutures superiorly to soft palate and retromolar trigone mucosa to maintain its orientation and avoid any twisting of the pedicle. The microvascular anastomosis is performed with loupe or surgical magnification depending on surgeon preference. After establishing reperfusion to the flap, the flap is inset with interrupted 3–0 Vicryl sutures using an RB-taper needle. When possible, the sutures should be passed by hand into the oropharynx. The da Vinci robot is brought into the field to achieve suturing that is not possible using the conventional nonrobotic approach. Robotic assistance allows placement of the sutures in the constricted field.

13.9.3 Perioperative Management

When performing transoral robotic free flap reconstruction, we perform a tracheostomy and place a nasogastric feeding tube at the time of the surgery if the patient does not have a gastric feeding tube. The patient’s flap is monitored with an implantable Doppler (Cook Medical) on the artery, and the flap can usually be inspected orally by performing a flexible fiberoptic nasopharyngoscopy. The Doppler is maintained for 5 days.
Reconstruction of the Oropharynx

On the third postoperative day, the tracheostomy is downsized and capping trials are performed on day 4 to allow the upper airway swelling to subside. The patient is usually decannulated on day 5 to 7 postoperatively. After decannulation, the patient works with the speech therapist on swallowing rehabilitation. Depending on the swallowing ability, the patient may have the feeding tube removed at time of discharge or later as an outpatient. The patient’s length of stay is usually 7 days after these procedures.

Note

The advantage of transoral robotic reconstruction is that it obviates the need for a midline mandibulotomy. This preserves the muscle attachments and aids in a faster functional recovery.

13.9.4 Pearls

For cases with deep tumor extension inferiorly to the bottom of the vallecula or when the transoral exposure is difficult, a hybrid approach can be performed. The hybrid approach consists of a lateral pharyngotomy at the level of the hyoid for the inferior aspect and the transoral robotic approach for the superior aspect of the resection. The advantages of this hybrid approach are that it allows for the safe resection and reconstruction of complex oropharyngeal defects in difficult-to-expose patients or patient with larger tumors.

13.10 Conclusion

Transmandibular surgery for oropharyngeal cancer used to be fraught with disastrous functional outcomes despite being effective at achieving disease control. Because of the morbidity associated with open surgical approaches to the oropharynx, nonsurgical therapy gained popularity. The refinement of transoral minimally invasive surgery has expanded the options for minimally invasive reconstructive approaches. The reconstructive surgeon is now able to choose the best reconstructive option based on the defect, patient factors, and his/her expertise. Ultimately the goal is to achieve oncologic control and restore function to the patient. Robotic and minimally invasive approaches do not require disarticulation of the pharyngeal muscles often required during the surgical approach. As a result, functional recovery is faster and often more complete than when traditional approaches are applied. Irrespective of the surgical approach, oropharyngeal reconstruction is a challenging endeavor that requires critical thinking to identify the best donor site and recognize the patient’s comorbid limitations. An understanding of the physiology of swallowing, speech, and an understanding of the airway dynamics is crucial on the part of the surgeon. An experienced reconstructive surgeon contemplates well beyond the task of reconstructing the soft tissue defect. Reestablishing the velopharyngeal unit, reconstituting the base of tongue volume, and preserving mobility and function of the pharyngeal phase of swallowing are all critical elements that must be considered. The task has become even more complicated in the face of salvage surgery. This chapter serves to highlight each of these critical elements and provide thoughtful approaches to the complexity of oropharyngeal reconstruction.

References


14 Carcinoma of the Hypopharynx

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14.1 Introduction

Malignancies of the hypopharynx are relatively rare, causing roughly 5% of all head and neck squamous cell carcinomas (SCCs).\(^3,4\) The treatment paradigm is continuously shifting, from a previous era of “radical” open surgery (e.g., total laryngopharyngectomy) toward a preference for organ-preservation strategies. Primary treatment options may include conservative/transoral surgical resection, altered fractionation radiation therapy, or combined modality chemotherapy with radiation. A variety of technological innovations developed over the past two decades are helping to optimize treatment efficacy while potentially improving patient functional outcomes. Newer radiation therapy techniques, including intensity-modulated radiation therapy (IMRT) and image-guided radiotherapy (IGRT), improve the dose delivered to the tumor while sparing normal tissues. Surgical advances, including advanced reconstructive techniques and more recently transoral robotic procedures, are potentially allowing decreased operative morbidity, shorter inpatient stays, and a greater likelihood of functional preservation.

With multiple treatment options, there remains a lack of high-level evidence to guide optimal management.\(^3\) The literature on hypopharyngeal cancer is most often limited to retrospective reviews with relatively small numbers of patients. Comparisons between studies are difficult because of changes in the staging system over time, inclusion of different subsites, selection bias related to different treatment modalities, and lack of uniform management algorithms.\(^1,2\) Treatment decisions for these complex tumors should thus incorporate a multidisciplinary team of surgical, radiation, and medical oncologists; radiologists; pathologists; and paramedical disciplines such as speech therapy, nutrition, nursing, and social work. This chapter reviews the presentation, diagnosis, and multidisciplinary management of SCC of the hypopharynx. Rather than providing an exhaustive summary of all studies on the different therapeutic approaches, our goal is to provide a general overview of treatment options available and their indications. An in-depth review of hypopharyngeal reconstruction is presented in a separate chapter.

14.2 Epidemiology

Carcinoma of the hypopharynx is uncommon in North America, accounting for 4.3 to 7% of all head and neck cancers with an overall incidence of 1 per 100,000 cases per year.\(^3,4\) This varies worldwide with the highest rate in France at 9.4 per 100,000 per year.\(^4\) Based on the Surveillance, Epidemiology, and End-Results (SEER) database, there has been a decrease in incidence over the past three decades.\(^4,7\) In the United States 78% of cases occur in males, with the majority affecting individuals in the sixth and seventh decades of life.\(^3,4,8\)

More than 95% of all hypopharyngeal malignancies are SCCs, which are often poorly differentiated.\(^2,3,4,9\) Adenocarcinomas account for the majority of the remaining 5% of hypopharyngeal malignancies; however, other rare neoplasms such as malignant fibrous histiocytoma, liposarcoma, synovial sarcoma, and mucosal melanoma have been reported.\(^9,10,11\) The hypopharynx is divided into three distinct anatomical subsites. According to SEER data, tumors are most commonly encountered within the paired pyriform sinuses (65%) followed by the posterior pharyngeal wall (25–35%), and less commonly postcricoid region.\(^6\) In North America, the ratio of pyriform sinus to postcricoid neoplasms is roughly 19:1.\(^4,8,14\)

14.3 Etiology

Potential environmental risk factors associated with hypopharyngeal SCC include tobacco/alcohol consumption, nutritional deficiencies, oncogenic viral infection, and rare occupational exposures. Tobacco use is, however, the most prominent etiologic factor in these (> 90% of patients).\(^7,12,15\) High rates of alcohol abuse (> 70% of cases) are generally also reported, which is known to have a synergistic carcinogenic effect with tobacco.\(^2,12,16,17\) Smoking/alcohol cessation is important to emphasize, as it is associated with substantial risk reduction and decreased likelihood of second primary lesions after initial hypopharyngeal cancer treatment.

There is a unique association between hypopharyngeal carcinoma and Plummer-Vinson syndrome (also termed Paterson-Brown-Kelly syndrome).\(^18,19,20\) The syndrome is characterized by dysphagia (caused by hypopharyngeal/esophageal webs), weight loss, and chronic iron-deficiency anemia. Additional findings include cheilitis, tooth loss, and glossitis.\(^18,19,20\) When developing malignancy, the classic patient is a 30- to 50-year-old woman, with no known tobacco/alcohol history, presenting with a postcricoid tumor. The key to this syndrome is early diagnosis and treatment of the underlying iron/vitamin B deficiency, which will prevent progression to malignancy.\(^19\)

Chronic infection with oncogenic viral strains, particularly of human papillomavirus (HPV) and Epstein-Barr virus (EBV), is known to cause upper aerodigestive tract malignancies. Over the past few decades, HPV infection has become particularly common and now related to a substantial percentage of oropharyngeal SCCs. Detection rates of high-risk HPV strains in hypopharyngeal carcinoma patients, however, has been relatively uncommon (< 10–20%).\(^21,22\) The fraction of these malignancies attributed to HPV is thus presumed to be low, and the clinical significance is uncertain.\(^21,22\) EBV viral infection also appears to have no or limited association with these carcinomas.\(^4,23\)

Note

A unique cause of hypopharyngeal carcinoma is Plummer-Vinson syndrome. It is characterized by hypopharyngeal or esophageal webs, weight loss, and chronic iron-deficiency anemia.
14.4 Hypopharyngeal Anatomy and Patterns of Disease Spread

14.4.1 Anatomical Associations

The subsite anatomy of the hypopharynx is detailed in Fig. 14.1. This region sits posterior/lateral to the laryngeal framework extending from the hyoid (superiorly) to the lower border of the cricoid where it is contiguous with the cervical esophagus. The pyriform sinuses conceptually are like inverted pyramids situated lateral to the larynx with their base superior and the lateral/anterior walls tapering to an inferior apex. The limit superiorly is the pharyngoepiglottic fold and the free margin of the aryepiglottic fold. The medial wall is formed by the lateral surface of the aryepiglottic fold and arytenoids, posterior ventricle, and lateral aspect of the cricoid cartilage. The lateral wall is bounded superiorly by the thyrohyoid membrane and inferiorly by the thyroid cartilage.

The posterior pharyngeal wall is bound by the inferior constrictor muscle. It extends from the level of the hyoid bone to the inferior border of the cricoid and from the apex of one pyriform sinus to the other. Posteriorly, it is related to the bodies of the third through sixth cervical vertebrae. Potential spaces separate the posterior pharyngeal wall from the prevertebral fascia, vertebrae, and attached spinal musculature. The postcricoid region is bounded anteriorly by the cricoid cartilage and arytenoids. Inferiorly, it is contiguous with the cervical esophagus. Important relations include the cricoarytenoid joints, the intrinsic laryngeal muscles, and the recurrent laryngeal nerves.

The sensory innervation of the hypopharynx is by the glossopharyngeal and vagus nerves via the pharyngeal plexus, superior laryngeal nerves (SLNs), and recurrent laryngeal nerves (RLNs). The internal branch of the SLN synapses in the jugular ganglion along with vagal branches from the middle ear (Arnold’s nerve), thus accounting for the referred otalgia seen in patients presenting with hypopharyngeal cancer. Motor innervation is from the pharyngeal plexus and RLNs. The vascular supply is from the superior laryngeal, lingual, and ascending pharyngeal arteries.

14.4.2 Local Patterns of Spread

Hypopharyngeal carcinomas have a tendency for multisite spread, particularly with large and undifferentiated tumors. For pyriform sinus malignancies, medial tumors tend to invade the larynx (Fig. 14.2). Lateral spread results in thyroid cartilage invasion while inferolateral extension can cause extension through the cricothyroid membrane leading to involvement of the cricoid cartilage, thyroid gland, or other extralaryngeal cervical tissue.

Fig. 14.1 Subsites of the hypopharynx. The hypopharynx is located posterior and lateral to the laryngeal framework extending from the hyoid (superiorly) to the lower border of the cricoid where it is contiguous with the cervical esophagus. The pyriform sinuses are inverted pyramids situated lateral to the larynx with their base superior and the lateral and anterior walls tapering to an inferior apex. The superior limit is the pharyngoepiglottic fold and the free margin of the aryepiglottic fold. The medial wall is formed by the lateral surface of the aryepiglottic fold and arytenoids, posterior ventricle, and lateral aspect of the cricoid cartilage. The lateral wall is bounded superiorly by the thyrohyoid membrane and inferiorly by the thyroid cartilage.

Fig. 14.2 For pyriform sinus malignancies (A), tumors are medial and thus spread inward (arrow) invading the larynx. For tumors involving the lateral pharyngeal wall (B), the tumor will tend to invade the thyroid cartilage and then escape the laryngeal framework (arrow). More posteriorly localized postcricoid tumors (C) will have a pathway out of the larynx via the cricothyroid membrane (arrow) allowing involvement of the cricoid cartilage, thyroid gland, and/or other extralaryngeal cervical tissue.
extralaryngeal cervical tissues.

Thyroid gland invasion occurs in 10% of hypopharyngeal carcinomas and is most likely in tumors with a postcricoid or subglottic component given a more direct pathway of spread outside the confines of the laryngeal framework. When surgical extirpation is being performed, hemithyroidectomy is often a necessary consideration when these features or other indicators of extralaryngeal spread (e.g., thyroid cartilage invasion or previous tracheostomy) are present. Large pyriform sinus tumors may extend to the base of the tongue, soft tissues of the neck, posterior pharyngeal wall, or across the postcricoid region to the contralateral pyriform. Invasion of the intrinsic laryngeal muscles, cricoarytenoid joint, and recurrent laryngeal nerves can all result in vocal cord immobility.

Posterior pharyngeal wall tumors tend to remain isolated to the posterior wall spreading either superiorly or inferiorly, although only rarely involve the cervical esophagus. Locally invasive, however, these lesions can involve the prevertebral fascia or vertebral bodies limiting treatment options. Postcricoid lesions on the other hand frequently invade surrounding structures, including the arytenoids, intrinsic laryngeal muscles, RLNs, and cricoid cartilage. Inferiorly, the tumor may extend to the cervical esophagus or invade the trachea.

Hypopharyngeal tumors, particularly postcricoid tumors, are notorious for the presence of skip lesions and extensive submucosal spread, which have been demonstrated in up to 60% of specimens. The extent of submucosal spread is greatest in the inferior direction (up to 30 mm) followed by the lateral direction (between 10 and 20 mm) and least in the superior direction (between 5 and 10 mm). It is important to note that these features may not be macroscopically evident, particularly after radiotherapy.

**Regional Patterns of Spread**

The hypopharynx demonstrates a particularly rich network of lymphatic channels accounting for the high rate of regional disease. Lymphatics from the pyriform sinuses drain through the thyrohyoid membrane following the superior laryngeal neurovascular pedicle to the jugulodigastric, midjugular (levels II and III), and retropharyngeal nodes. Lymphatics of the posterior pharyngeal wall pierce the inferior constrictor muscle and drain to the retropharyngeal and upper jugular nodes (level II), whereas lymphatics of the postcricoid region tend to follow the RLNs to the paratracheal, paraesophageal, and lower jugular nodes (level II), with, on occasion, extension to the posterior mediastinal nodes. The posterior pharyngeal wall, postcricoid, and the medial pyriform sinus have bilateral lymphatic drainage patterns.

**Staging**

The TNM classification set forth by the American Joint Committee on Cancer (AJCC) is the main staging system used for hypopharyngeal SCC. The prognosis for patients with hypopharyngeal cancer is poor, with comparably lower survival rates (per stage) than most other upper aerodigestive tract malignancies. Explanations include late stage at presentation, early invasion of surrounding structures (lack of boundaries to tumor spread), frequent nodal/distant metastases, and a higher than average rate of synchronous malignancies.
Adverse patient-specific features including advanced age, multiple confounding medical comorbidities, generally low socioeconomic status, and poor pretreatment nutritional status are also common.\textsuperscript{17,24} In addition to the late stage at presentation, specific features of these malignancies, in particular, submucosal spread and multicentricity, create unique technical challenges.\textsuperscript{1,12,13,14,33,34} Despite these issues, there has been a subtle trend for improved 5-year survival (SEER data) increasing to 41.3\% by 2003 from 37.5\% in 1990.\textsuperscript{8}

### 14.6 Presentation

#### 14.6.1 History

Hypopharyngeal cancers tend to remain asymptomatic for a long period of time with the majority of patients presenting with locally advanced disease. Between 70 and 84\% of patients present with either T3 or T4 disease and more than 70\% with stage III or IV disease.\textsuperscript{4,12,13,17,37} Palpable nodal metastases are detectable in 50 to 75\% of patients at presentation.\textsuperscript{4,13,37,38,39} Symptoms occur when the tumor reaches considerable size or invades surrounding structures and include progressive dysphagia, neck mass, odynophagia, and otalgia.\textsuperscript{8,38}

Less frequent symptoms include hoarseness, hemoptysis, cough, and weight loss. Patients with large retropharyngeal nodes may present with occipital or posterior neck pain radiating to the retro-orbital region.\textsuperscript{24} Other important elements of the history include nutritional status, comorbidities, and tobacco and alcohol consumption.

#### 14.6.2 Physical Examination

The physical examination should focus on assessing the extent of the primary tumor, detecting regional disease, and excluding a synchronous malignancy. On flexible endoscopy, hypopharyngeal lymphatics from the piriform sinuses drain through the thyrohyoid membrane following the superior laryngeal neurovascular pedicle to the jugulodigastric, midjugular (levels II and III), and retropharyngeal nodes. Lymphatics of the posterior pharyngeal wall pierce the inferior constrictor muscle and drain to the retropharyngeal and upper jugular nodes (level II), whereas lymphatics of the postcricoid region tend to follow the recurrent laryngeal nerves to the paratracheal, paraesophageal, and lower jugular nodes (levels IV and VI), with, on occasion, extension to the posterior mediastinal nodes.

### Table 14.1 Outline of American Joint Committee on Cancer staging for hypopharynx cancer: hypopharynx

<table>
<thead>
<tr>
<th>a. Primary tumor (T)</th>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to one subsite of the hypopharynx and ≤ 6.2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades more than one subsite of the hypopharynx or an adjacent site, or measures &gt; 2 cm but not &gt; 4 cm in greatest dimension without fixation of the hemilarynx or extension to the esophagus</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 4 cm in greatest dimension or with fixation of the hemilarynx or extension to the esophagus</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue*</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures</td>
</tr>
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Note: The hypopharynx includes the pyriform sinuses, the lateral and posterior hypopharyngeal walls, and the postcricoid region. *Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat. (Continued)
Yngeal malignancies tend to appear as either an ulcerative or infiltrative lesion. Exophytic lesions are less common and tend to occur on the posterior pharyngeal wall. Pooling of secretions suggests pyriform sinus apex or cervical esophageal involvement. Examination of the larynx and assessment of vocal cord mobility are important for staging, prognosis, and treatment planning. Postcricoid tumors may be difficult to visualize if they have caused significant mucosal edema of the posterior larynx. As they enlarge, they displace the larynx forward producing a fullness in the anterior neck and loss of the palpable clicking that occurs when one rocks the larynx from side to side.

### 14.7 Diagnosis and Workup

#### 14.7.1 Panendoscopy and Biopsy

Pathologic confirmation and adequate tumor mapping is necessary prior to treatment of hypopharyngeal carcinomas. When cervical adenopathy is present, in-office fine-needle aspiration biopsy can be performed. Panendoscopy under general anesthesia allows assessment of the full extent of the tumor, which helps with treatment planning and allows detection of synchronous primaries. Information obtained will influence treatment decisions and provide valuable information for the surgeon about the extent of resection and method of reconstruction. Deep fixation of posterior pharyngeal wall tumors may be assessed by moving the tumor on the cervical spine.

#### 14.7.2 Diagnostic Imaging and Metastatic Survey

Computed tomography (CT) and/or MRI should be used to assess the tumor extent, nodal status, and potential laryngeal/paraglottic space involvement or cartilage invasion. Tumors additionally found to be encasing the carotid artery, invading the cervical spine, or skull base on imaging are generally incurable even with radical resection. In assessing invasion of the laryngeal cartilages, CT is particularly valuable and is more specific than MRI. The CT will often demonstrate effacement of...
the normal tissue planes (▶ Fig. 14.5). Occult submucosal disease, tumor spread along the superior laryngeal neurovascular pedicle, involvement of the intrinsic laryngeal musculature, and deep extension into the paraglottic and preepiglottic spaces may be detectable on MRI.\textsuperscript{41} MRI and CT are complementary examinations providing detailed cross-sectional anatomy of the hypopharynx and tumor growth patterns that will aid in the detection and evaluation of the full extent of the tumor.

Positron emission tomography (PET) combined with CT (PET/CT) has a role in the pre- and posttreatment workup. It is felt to have a supplementary role to anatomical imaging, particularly useful for confirmation of primary tumor location (in low-volume disease) as well as the identification of cervical or distant metastatic disease. The limitations of PET/CT, however, include false-positive results (due to active inflammation), high cost, and potentially limited availability. It is important to note that hypopharyngeal carcinomas have a particularly high rate of both nodal and distant (ranging from 6 to 24\% in reported series) metastatic spread, when compared to other head and neck malignancies.\textsuperscript{12,38,42,43,44} The most common sites of distant dissemination include the pulmonary parenchyma (> 50\%), mediastinal nodes, liver, and bone.\textsuperscript{42}

**14.8 Prognostic Factors**

Hypopharyngeal SCC has the worst prognosis of all head and neck SCCs, with 5-year overall survival rates ranging from 15 to 45\%.\textsuperscript{1,4,7,12} Data from the Swedish Cancer Registry, for example, reporting outcomes from 1960–1989, identified an overall survival rate of 15\% for all patients.\textsuperscript{45} US data from a similar time period, taken separately from the National Cancer (1985–1989) and SEER databases, identified 5-year survival rates from 31 to 33\%.\textsuperscript{4,7} More recent population-based data detailing the management of 595 patients in Ontario, Canada from 1990–1999 report a similar 35\% 5-year disease-specific survival rate for those receiving curative treatment.\textsuperscript{17}

The largest study to date of hypopharyngeal malignancies, reported by Hoffman et al, assessed 1,317 patients across multiple American hospital systems in the 1980s and 1990s. Overall 5-year disease-specific survival for all patients was 33.4\%, with stage-specific outcomes also reported as follows: stage I, 63.1\%; stage II, 57.5\%; stage III, 41.8\%; and stage IV, 22\%.\textsuperscript{12} All known adverse prognostic factors (including stage) are presented in ▶ Table 14.2. The most important predictors of disease-specific survival are cervical lymph node status (N classification) and size of the primary tumor (T classification).\textsuperscript{13,46,47} When determining the overall prognosis of this population, other factors such as advancing patient age, medical comorbidities, functional status, substance abuse, etc. also need to be considered.\textsuperscript{46} As noted previously, there is also a relatively common likelihood of second upper aerodigestive tract primary lesions (7% at presentation and then 2.3\% per year) and distant metastatic spread.\textsuperscript{12,44,46,48} When disease dissemination is present, it will generally occur within 9 months of initial diagnosis and impact the lung, liver, mediastinum, and bone.\textsuperscript{42,44} The median survival of patients with distant metastases is under 1 year.\textsuperscript{49}

**14.9 Treatment**

When considering the initial management strategy for hypopharyngeal malignancy, three main options are available: (1) primary surgical resection, (2) radiation therapy, and (3)
planned concurrent (or alternating) radiotherapy + chemotherapy. Treatment selection requires balancing a desire for anatomical preservation of tissue and disease cure while also attempting to optimize aerodigestive tract functioning in order to prevent chronic aspiration and permanent tracheostomy/feeding tube dependence. There are few randomized controlled trials comparing different therapeutic modalities in hypopharyngeal cancer. Given this, an understanding of the breath and inherent limitations of the available literature must be recognized when making treatment decisions.

### 14.9.1 Overall Treatment Philosophy

#### Early-Stage Disease (T1/T2 with N0/N1)

The ideal management for early-stage tumors is an area of significant debate with both primary radiotherapy or conservative surgical approaches deemed as valid options. Locoregional control (LRC) and survival rates are similar for both, however, prospective evidence comparing these modalities is limited. For example, many prominent organ-preservation trials, including those performed through the US Department of Veterans Affairs (VA), European Organization for Research and Treatment of Cancer (EORTC), or Radiation Therapy Oncology Group (RTOG), have focused on laryngeal malignancies, excluding primary hypopharyngeal disease. Studies of individual modalities must also be reviewed cautiously, given an inherent patient selection bias that may limit generalizability to the population as a whole.

#### Note

Most organ-preservation trials (Veterans Affairs, EORTC, and RTOG) have focused on laryngeal malignancies, excluding primary hypopharyngeal disease. It is therefore difficult to extrapolate findings from these studies to hypopharyngeal disease.

In early-stage patients, both surgery and radiotherapy have the potential for anatomical/functional preservation of impacted regions within the head and neck. Experience with radiation (often including concurrent chemotherapy) is more established, with 5-year laryngeal preservation rates of greater than 70% reported. Innovation in transoral surgical techniques/instrumentation is, however, making primary tumor resection an increasingly viable option. Proponents of surgery allude to the potential for improved laryngeal preservation rates (> 80%) achieved in a number of single-institution series (> Table 14.3). Those who advocate for the utilization of radiation therapy for early-stage disease suggest that better functional outcomes are possible with this modality. It is also important to note that for patients treated with primary surgery, postoperative radiotherapy is often required to optimize disease control, which presumably increases the overall treatment-related toxicity (compared with radiotherapy alone).

#### Advanced-Stage Disease (T3/T4 or ≥ N2)

Optimal treatment for advanced-stage hypopharyngeal carcinoma, based on control/survival rates, includes concurrent chemoradiotherapy, altered fraction radiation (e.g., hyperfractionated radiation delivered with integrated neck surgery [HARDWINS]), or surgery + adjuvant radiotherapy. Nonsurgical therapy is generally advocated when an organ-preservation approach is presumed possible, due to the associated morbidity of extensive partial laryngeal/laryngopharyngeal resections. However, rates of functional laryngeal preservation for those with the most advanced local disease (e.g., gross cartilage invasion, vocal fold fixation, or pretreatment tracheostomy dependence) are more limited. Even when rendered disease-
free, these patients are often left tracheostomy/feeding tube
dependent, and thus may be better served by total laryngo-
pharyngectomy. Induction chemoselection has been proposed
as a novel method of identifying advanced lesions (including T4
disease) most likely to be appropriate for an organ-preservation
strategy; however, this approach has not yet been broadly
adopted.48,62

14.9.2 Surgical Approaches

Open Surgical Procedures

A wide array of different hypopharyngeal surgical procedures
has been historically described (▶ Table 14.4). For low-volume
disease (T1/T2), a partial pharyngectomy can be performed
through either a median labiomandibular glossotomy, trans-
hyoid pharyngotomy, lateral pharyngotomy, or combined
approach. In most instances, however, these techniques have
been replaced either with primary radiotherapy or transoral
techniques. More locally advanced tumors (T3/T4) require a for-
mal pharyngectomy combined with either a partial or total lar-
yngectomy (+/- an additional complex reconstruction).

<table>
<thead>
<tr>
<th>Table 14.4 Open surgical approaches for hypopharyngeal carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Larynx preservation</strong></td>
</tr>
<tr>
<td>Partial hypopharyngectomy</td>
</tr>
</tbody>
</table>
| Median labiomandibular
glossotomy | |
| Trans(supra)hyoid pharyngotomy | |
| Lateral pharyngotomy | |
| Combined approach ±
mandibulotomy | |
| Partial laryngectomy with
pharyngectomy | Total (circumferential) |
| Vertical hemilaryngectomy and
pharyngectomy | Laryngopharyngectomy |
| Supraglottic laryngectomy and
pharyngectomy | |

T1/T2 Tumors

Superiorly placed tumors (e.g., posterior pharyngeal wall) may
be approached through a transhyoid pharyngotomy or median
labiomandibular glossotomy.63,64 The transhyoid approach is
performed by dividing the suprahoid musculature and either
depressing the hyoid bone or excising its central portion for
pharyngeal entry (▶ Fig. 14.6). The tumor can then be excised
locally with primary closure or skin grafting. The median labio-
mandibular glossotomy gives extensive exposure of this region
for tumors that cannot be adequately visualized by a transhyoid
approach. It involves a lip split, mandibulotomy, and division of
the tongue along the midline raphe.63,64 While facilitating wide
exposure, this can result in extensive postoperative morbidity
and has thus been largely abandoned.45,63,64

Lateral pharyngotomy is a more versatile approach that
entails mobilization of the entire laryngopharyngeal complex
unilaterally via longitudinal incision into the pyriform sinus
behind the thyroid ala.45,64 A specific attempt should be made
during this maneuver to identify/preserve the internal branch
of the superior laryngeal nerve. This provides access to all sub-
sites of the hypopharynx but is most suitable for tumors of the
lateral pyriform sinus or inferior posterior wall. Aspiration may
be an issue for extensive resections (e.g., vocal cord paralysis or
excessive bulk from reconstruction), and thus it should not be
used for advanced disease. This approach may still have a role
(particularly in the salvage setting) for low-volume disease that
cannot be exposed transorally.45

T3/T4 Tumors

Locally advanced tumors can be addressed by a variety of surgical
approaches. Assessment of pretreatment pulmonary reserve
is important, as conservation laryngeal procedures will cause a
certain degree of inevitable postoperative aspiration. Another
important consideration is planned extent of resection margins,
particularly inferiorly (esophageal margin).2,28,33,34 Concern
over skip lesions and submucosal disease invasion requires
wide margins; however, studies have demonstrated no benefit
in local control or survival for extended (3–5 cm) versus tradi-
tional (1–1.5 cm) margins. This equivalence is likely related to
Carcinoma of the Hypopharynx

Table 14.5 Contraindications for laryngeal preservation surgery

<table>
<thead>
<tr>
<th>Vertical partial laryngopharyngectomy</th>
<th>Horizontal partial laryngopharyngectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral cricoarytenoid unit involvement (fixed/impaired vocal fold)</td>
<td>Fixed bilateral arytenoids/vocal folds</td>
</tr>
<tr>
<td>Paraglottic or preepiglottic space invasion</td>
<td>Posterior tumor with involvement of 1. Interarytenoid space 2. Posterior commissure 3. Mucosal surface of bilateral arytenoids</td>
</tr>
<tr>
<td>Thyroid cartilage invasion</td>
<td>Preepiglottic space invasion</td>
</tr>
<tr>
<td>Involvement of one-third of the contralateral vocal fold</td>
<td>Subglottic extension</td>
</tr>
<tr>
<td>Extensive thyroid/cricoid cartilage invasion</td>
<td>Hyoid invasion or extralaryngeal spread</td>
</tr>
</tbody>
</table>

The utilization of adjuvant radiotherapy in the majority of patients with advanced-stage disease.

Partial pharyngeal resection may be combined with conservation laryngeal resections (vertical hemilaryngectomy, supraglottic laryngectomy, or supracricoid laryngectomy) to address a range of small-to-moderate-sized hypopharyngeal carcinomas. Lacourreye et al have published a particularly extensive experience with these approaches. Their most recent series details 135 patients with pyriform sinus malignancies managed by induction chemotherapy (IC) (96%) and supracricoid hemilaryngopharyngectomy. Five-year actuarial survival was estimated at 46.7%, with tracheostomy decannulation possible in all patients (mean = 9 days), and a 91.9% resumption of oral alimentation (without gastrostomy) at 1 year. The key to successful open partial surgical procedures is an understanding of the cricoarytenoid unit, composed of (1) a single arytenoid, (2) cricoid, (3) ipsilateral recurrent/superior laryngeal nerves, and (4) ipsilateral intrinsic laryngeal muscles. Appropriate upper aerodigestive tract function requires that at least a single functional outcome be preserved. Contraindications to vertical or horizontal partial laryngeal procedures that compromise the cricoarytenoid unit are detailed in Table 14.5.

For the most advanced hypopharyngeal tumors (e.g., T4 with cartilage invasion, vocal fold fixation, and/or esophageal extension), a total laryngectomy + partial versus circumferential pharyngectomy will thus be required to optimize oncologic and functional outcomes. Posttreatment, speech therapy is necessary as most patients will be appropriate candidates for tracheoesophageal puncture, allowing a high likelihood (>90%) of intelligible speech production.

As previously outlined roughly 10% of hypopharyngeal carcinomas will have direct extension into the thyroid parenchyma. A hemithyroidectomy or total thyroidectomy (patients with gross extralaryngeal tumor invasion) will thus be required in a subset of patients. In the salvage setting, preoperative hypothyroidism must also be ruled out, due to the impact of radiotherapy on thyroid vasculature with resultant thyroid dysfunction. In a prospective longitudinal series of 137 laryngeal/hypopharyngeal patients, Lo Galbo et al reported a 47.4% incidence of eventual posttreatment hypothyroidism, raising to as high as 80% in postoperative patients.

Routine pre- and postoperative screening of thyroid hormone with early replacement, when appropriate, is thus essential in this population. Hypoparathyroidism is also a likely concern after circumferential pharyngeal resection and/or paratracheal + mediastinal node dissection. Consequently, parathyroid identification and preservation or reimplantation are important.

Transoral Approaches

While initially described over 50 years ago, utilization of the transoral route for access to the upper aerodigestive tract has become increasingly popularized over the past few decades. Transoral laser surgery (TOLS), in particular, was initially popularized for laryngeal carcinoma, but later extended for hypopharyngeal malignancies. Reported advantages over conventional surgical resection include decreased incidence of intraoperative tracheostomy, faster postoperative functional recovery, shortened hospital stay, and lower cost. Local control and recurrence-free survival rates, particularly for T1/T2 lesions, have importantly also mirrored those achieved with radiotherapy alone and open conservation surgery. A series by Karatzanis et al of 119 patients with T1 and T2 lesions had 5-year disease-specific survival and local control rates of 72.6 and 85.4%. This was achievable with long-term tracheostomy and gastrostomy dependence rates of only 2.5%. However, as is the case in other TOLS series, oncologic outcomes required adjuvant treatment (radiotherapy or concurrent chemoradiotherapy) in 83% of patients.

Table 14.5

<table>
<thead>
<tr>
<th>Contraindications for laryngeal preservation surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical partial laryngopharyngectomy</td>
</tr>
<tr>
<td>Horizontal partial laryngopharyngectomy</td>
</tr>
</tbody>
</table>

The advantages of TOLS include decreased incidence of intraoperative tracheostomy, faster postoperative functional recovery, shortened hospital stay, and lower cost.

After a TOLS resection, the surgical defect is left to granulate and remucosalize. Theoretically, this has the advantage of restoring a patent pyriform sinus, but can also cause obliteration with continuity of the endolarynx/pharynx leading to some degree of chronic aspiration. Other procedural complications include fistula, granulation tissue formation, and the potential for postoperative bleeding which can lead to fatal airway obstruction. This is generally addressed by synchronous neck dissection with ligation of the arterial supply to this region (generally the ascending pharyngeal and lingual arteries). Low-volume lesions, particularly of the lateral pyriform sinus and posterior pharyngeal wall, are best candidates for transoral resection. Medial pyriform and postcricoid disease is more difficult to expose and may require more extensive resection of the paraglottic space, supraglottic structures, and cricoarytenoid complex/recurrent laryngeal nerve. Data detailing the use of TOLS for locally advanced disease (T3, T4) are limited, and thus the potential role (if any) for these cases remains poorly explained.

Over the past few years, literature on transoral robotic surgery (TORS) for hypopharyngeal carcinoma has slowly begun to develop. The potential benefit of TORS versus TOLS is enhanced visualization and exposure afforded by the robotic
instrumentation. Theoretically TORS enhances the ability to perform an en bloc partial hypopharyngectomy without the “line of sight” limitations of transoral microsurgery.143,166 Despite the growing popularity of TORS for oropharyngeal malignancy, the published literature for hypopharyngeal carcinoma is limited to a handful of case reports and feasibility trials. While this approach shows promise, its role in the management of hypopharyngeal carcinoma will remain unclear until more comprehensive data become available.84,85,86

14.10 Management of the Neck

14.10.1 Nodal Metastases

There is a high likelihood of cervical lymph node metastasis in virtually all patients with hypopharyngeal carcinoma.87,88 Pyriform sinus cancers have the highest rate of neck metastases, (>75% of patients) compared to posterior pharyngeal wall and postcricoid cancers where the rate of nodal metastases ranges between 30 and 60% at presentation.42,87,88,89 When a primary surgical approach is undertaken, the at-risk cervical lymph node basins must thus be dissected, when a clinically negative (cN0) neck is encountered. For large tumors that cross the midline and those arising from the posterior pharyngeal wall, medial wall of pyriform, or postcricoid region, bilateral neck dissection is advisable.36,88

Note

There is a nearly 75% likelihood of cervical lymph node metastasis in patients with hypopharyngeal carcinoma. As a result, treatment of the neck is mandatory.

In the cN0 setting, any microscopically positive cervical adenopathy will tend to be localized in the lateral neck at levels II and III.147,151,152 Thus levels II to IV should be addressed for elective neck dissection in these cases. In patients with clinical nodal metastases (cN+), a comprehensive neck dissection is indicated with inclusion of levels I through V. Although the incidence of metastases to levels I and V remains low, the risk increases to a level to consider their dissection. Sacrifice of the internal jugular vein (IJV), sternocleidomastoid muscle, and accessory nerve is only performed if they are directly invaded with cancer.

Particular attention must also be paid to retropharyngeal and paratracheal nodes (level VI) which are also at risk.1,144 Retropharyngeal nodal disease is particularly likely for posterior pharyngeal and lateral pyriform tumors, occurring in as many as 40% of patients with advanced T classification.35 These nodes are often difficult to address surgically, with the exception of laryngopharyngectomy cases. Retropharyngeal nodes should thus be considered during adjuvant radiotherapy planning and when clinically/radiographically positive at presentation, these are likely an indication for nonsurgical management when moderately advanced disease is present.35 Paratracheal nodal disease (level VI) is most common in tumors arising within the postcricoid region or pyriform apex.88,92,93,94,95 A recent series by Chung et al, for example, reports a 27.9% occult level VI nodes, with markedly poor prognosis in this group (26 vs. 55% 5-year disease-specific survival).95 Paratracheal node dissection should thus be strongly considered in this population both for tumor clearance and accurate disease staging.

Table 14.6 Common toxicities of radiation therapy

<table>
<thead>
<tr>
<th>Acute toxicity</th>
<th>Late toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized fatigue</td>
<td>Xerostomia</td>
</tr>
<tr>
<td>Altered sense of taste</td>
<td>Altered speech</td>
</tr>
<tr>
<td>Oral mucositis/esophagitis</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Significant dysphagia (requiring gastrostomy placement)</td>
<td>Esophageal/pharyngeal stricture</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>Neck fibrosis</td>
</tr>
<tr>
<td>Skin erythema</td>
<td>Laryngeal chondronecrosis</td>
</tr>
<tr>
<td>Alopecia (in irradiated volume)</td>
<td>Mandibular osteoradionecrosis (if included in radiation field)</td>
</tr>
</tbody>
</table>

14.11 Radiation Therapy

Over the past half century, improvements/standardization of radiotherapy techniques as well as an understanding of the need for dose escalation have dramatically expanded the utilization and effectiveness of radiation as a key treatment for these malignancies.37 For advanced disease, treatment may be further intensified by the application of alternate fractionation schemes or the addition of chemotherapy.36,97 In addition to dose escalation/ altered fractionation, technologic refinement has advanced the field of radiation oncology over the past two decades.52 This includes CT-based high-precision radiation planning/delivery (e.g., conformal radiotherapy and IMRT) and image-guided radiotherapy (IGRT). These techniques allow concentration of dose to the primary tumor while reducing collateral damage to surrounding tissues and reducing treatment-related morbidity.98 Emerging data have begun to demonstrate the promise of these newer “precision” techniques, with improved locoregional control of hypopharyngeal carcinoma, compared to standard therapy.52,98,99

Despite these refinements, radiation therapy continues to be associated with substantial acute and late toxicity (>Table 14.6). While most acute toxicities, such as radiodermatitis (>Fig. 14.7), are transient (improving within 6–12 weeks of treatment), a certain degree of permanent xerostomia is invariably experienced. Chronic dysphagia and aspiration may also occur posttreatment, requiring permanent feeding tube use; this risk is increased with intensified (e.g., concurrent chemoradiotherapy) regimen. The challenges posed by the current modern era of “precision radiotherapy” (particularly in low-volume centers) includes the necessity of “high-quality” radiotherapy, for the realization of reported benefit.100 The appropriate local expertise and effective quality assurance mechanism are thus required both to optimize outcome and limit treatment-associated toxicity.
14.11.1 Early-Stage Lesions (T1/T2 with N0/N1)

Control and survival rates after radiation therapy for early hypopharyngeal cancers are similar to those reported for surgery.\(^{50,51}\) As previously discussed, there are no prospective trials comparing primary radiotherapy with organ-sparing surgery in a head-to-head matter.\(^{1}\) For this reason, early-stage lesions need to be considered on a case-by-case basis in a multidisciplinary (tumor board) setting. Proponents for radiotherapy argue that functional outcomes are superior in terms of swallowing and speech when compared with surgery, although the evidence for this is limited. Another key drawback of conservation surgery is the high likelihood of requiring adjuvant radiotherapy (or chemoradiotherapy).

### Note

There are no prospective trials comparing primary radiotherapy with organ-sparing surgery in a head-to-head matter. As a result, early-stage lesions should be evaluated on a case-by-case basis in a multidisciplinary (tumor board) setting to determine the optimal treatment approach.

Local control rates after radiation therapy for T1 tumors range from 68 to 90% and roughly 75% for T2 lesions (\(\rightarrow\) Table 14.7).\(^{30,101,102,103}\) Disease-specific survival for these cases ranges from 50 to 100% at 5 years (\(\rightarrow\) Table 14.8). These results are achieved with conventional fractionation, 1.8 to 2 Gy per fraction to a total dose of 66 to 72 Gy over a 6- to 7-week course. Shorter treatment schemes, for example 2.5 Gy to a dose of 50 to 60 Gy over 4 to 5 weeks, can be used for patients whose comorbidities prevent a longer treatment course, but this will compromise disease control.

### Table 14.7 Local and ultimate \(^{a}\) control rates in early hypopharynx cancers managed with radiotherapy alone

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Case No.</th>
<th>Local Control</th>
<th>Ultimate Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meoz-Mendez et al(^{156})</td>
<td>1978</td>
<td>164 T1: 91%</td>
<td>T1: 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 73%</td>
<td>T2: 78%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3: 61%</td>
<td>T3: 71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T4: 37%</td>
<td>T4: 41%</td>
</tr>
<tr>
<td>Bataini et al(^{157})</td>
<td>1982</td>
<td>48</td>
<td>T1: 93%</td>
<td>T1: 100%</td>
</tr>
<tr>
<td>Dubois(^{158})</td>
<td>1986</td>
<td>60, 148</td>
<td>T1: 100%</td>
<td>T1: 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 73%</td>
<td>T2: 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3/A4: 73%</td>
<td></td>
</tr>
<tr>
<td>Fein et al(^{102})</td>
<td>1993</td>
<td>41, 88</td>
<td>T1: 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 74%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3: 49%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T4: 36%</td>
<td></td>
</tr>
<tr>
<td>Wang(^{159})</td>
<td>1997</td>
<td>105</td>
<td>T1: 88%</td>
<td>T1: 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 55%</td>
<td>T2: 83.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3–T4: 49%</td>
<td>T3: 56%, T4: 36%</td>
</tr>
<tr>
<td>Amdur et al(^{51})</td>
<td>2001</td>
<td>101</td>
<td>T1: 90%</td>
<td>T1: 95%</td>
</tr>
<tr>
<td>Hull et al(^{160})</td>
<td>2003</td>
<td>60</td>
<td>T1: 93%</td>
<td>T1: 93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 82%</td>
<td>T2: 87%</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td></td>
<td>T3: 59%</td>
<td>T3: 61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T4: 50%</td>
<td>T4: 50%</td>
</tr>
</tbody>
</table>

\(^{a}\)Ultimate control is considered final local control after surgical salvage of initial disease failure.

“High-risk” T2 tumors are defined as being greater than 2.5 cm or involving the pyriform apex, which do not respond well to conventional therapy.\(^{51,103}\) Altered fractionation schemes have been utilized in this setting with improvements in local disease control.\(^{50,51,104,105}\) Examples of schemes used include (1) 76 to 81.6 Gy in 1.2 Gy per fraction twice daily over...
6 to 7 weeks or (2) 64 Gy in 1.6 Gy per fraction twice daily over 4 weeks. The latter radiation schedule (HARDWINS) was investigated at Princess Margaret Hospital as an altered fractionation with reduced overall treatment time. In a dose escalation study of 60, 62, and 64 Gy delivered with twice-daily radiation therapy over 4 weeks, 64 Gy was found to be associated with acceptable toxicity when used in combination with a planned neck dissection for N+ disease (irradiated to lower doses).

14.11.2 Advanced Lesions (T3/T4, or Any T Stage with N2/N3)

Advanced-staged lesions are associated with local control rates between 38 and 80% and poor 5-year disease-specific survival (<25%) when treated with radiotherapy alone (see Table 14.8). Single-modality (standard fractionation) radiotherapy thus has a limited role in this setting reserved for patients who either refuse or cannot tolerate aggressive therapy with knowledge that disease-related outcomes are poor.1,57,61 To optimize locoregional control and patient survival treatment intensification with, for example, altered fraction radiation, concurrent chemoradiotherapy (CRT), or surgery + adjuvant radiotherapy is necessary.106,107 As there has generally been a shift toward organ-preservation approaches, nonsurgical approaches are often favored when appropriate.107 Alternate fractionation radiotherapy alone can be applied for moderately advanced disease (e.g., T2–T3, N0–N1). However, when stage IV malignancy is present, the addition of chemotherapy (either as a pretreatment induction strategy or currently with radiotherapy) is likely required to enhance treatment efficacy.107,108 Multimodality organ-preservation protocols are discussed in more detail in this chapter.

14.11.3 Adjuvant Radiotherapy

In patients managed with primary surgery, postoperative radiotherapy is almost always indicated for locally advanced tumors and those with locally early disease and high-risk features (e.g., positive margins, > N1 neck disease, extracapsular extension), as listed in Table 14.9. The addition of postoperative radiotherapy is associated with improved locoregional control, disease-free and overall survival in patients with advanced hypopharyngeal cancers.101,109,110,111,112 It is recommended that postoperative radiation be initiated 4 to 8 weeks after surgery. Longer delays may allow tumor proliferation and diminish the benefits of adjuvant radiation. We recommend that the primary site and bilateral necks be included in the radiation volumes with a dose of 60 Gy in 2 Gy per fraction. When positive margins or extracapsular nodal extension is present, 66 Gy should be provided to the high-risk areas to maximize control.109 For very-high-risk disease (positive margins or extracapsular margins), concomitant chemotherapy should be considered based on the results of recent randomized trials.113,114,115

### Table 14.8 Single-institution survival outcomes with definitive radiotherapy or chemoradiotherapy for hypopharyngeal carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Treatment</th>
<th>5-year OS</th>
<th>5-year DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bataini et al</td>
<td>1982</td>
<td>CRT</td>
<td>Stage I: 19%</td>
<td>Stage I: 41%</td>
</tr>
<tr>
<td>Fein et al</td>
<td>1993</td>
<td>CRT</td>
<td>Stage I: 50%</td>
<td>Stage I: 100%</td>
</tr>
<tr>
<td>Hull et al</td>
<td>2003</td>
<td>CRT</td>
<td>Stage I: 56%</td>
<td>Stage I: 89%</td>
</tr>
<tr>
<td>Tombolini et al</td>
<td>2004</td>
<td>CRT</td>
<td>Stage II: 42%</td>
<td>Stage II: 88%</td>
</tr>
<tr>
<td>Gupta et al</td>
<td>2009</td>
<td>CRT + chemo</td>
<td>Stage III: 52%</td>
<td>Stage III: 44%</td>
</tr>
<tr>
<td>Mok et al</td>
<td>2015</td>
<td>CRT + chemo IMRT</td>
<td>Stages I–IV: 51%</td>
<td>Stage I: 100%</td>
</tr>
<tr>
<td>Edson et al</td>
<td>2016</td>
<td>IMRT + chemo</td>
<td>Stages I–IV: 56%</td>
<td>Stage IV: 28.8%</td>
</tr>
</tbody>
</table>

Abbreviations: C-RT, conventional radiotherapy (e.g., parallel opposed fields); CRT, chemoradiotherapy; DSS, disease-specific survival; IMRT, intensity-modulated radiation therapy; OS, overall survival.

*Radiation schemes utilized both standard and hyperfractionation regimen.

Data provided are 3-year (not 5-year) survival outcomes.

### Table 14.9 Indications for postoperative radiotherapy

<table>
<thead>
<tr>
<th>Indications for radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced-stage disease (T3/T4)</td>
</tr>
<tr>
<td>Microscopically involved (or close &lt; 5 mm), resection margins</td>
</tr>
<tr>
<td>Pathologically N2 or N3 disease</td>
</tr>
<tr>
<td>Extracapsular nodal extension</td>
</tr>
<tr>
<td>Multiple intermediate risk factors such as the following:</td>
</tr>
<tr>
<td>1. Perineural invasion</td>
</tr>
<tr>
<td>2. Lymphovascular margin</td>
</tr>
<tr>
<td>3. Bulky primary (&gt;4 cm)</td>
</tr>
<tr>
<td>4. Close resection margins</td>
</tr>
</tbody>
</table>
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14.12 Chemotherapy

The addition of chemotherapy to radiation therapy in the management of locally advanced cancers of the head and neck has demonstrated locoregional control and survival rates better than radiation alone and comparable to combined surgery + radiotherapy.104,116,117 The main chemotherapeutic agent used for head and neck SCC is cisplatin with or without 5-fluorouracil (5-FU). When considering the utility of chemotherapy for any case, it must be recognized that organ-preservation strategies are not for all advanced cancers, necessitating careful patient selection.104 Those with significant baseline organ dysfunction and poor performance status are unlikely to do well. Patients with significant dysphagia at presentation, for example, will rarely improve after therapy. Pretreatment vocal cord fixation and tracheostomy dependence are additional predictors of poor posttreatment functional outcomes.118 When organ-preservation protocols are considered, the treatment goal must be maintenance of acceptable upper aerodigestive function, not simply perpetuation of the anatomical structures.26,119,120 The two major treatment strategies (in addition to altered fractionation radiotherapies) pursued in these protocols include IC and concurrent chemoradiotherapy.115

14.12.1 Concurrent Chemotherapy with Radiation

The standard schedule used in North America is cisplatin given at 100 mg/m² for three cycles on days 1, 22, and 43 with standard fractionation radiotherapy. Other schedules of combining cisplatin and radiotherapy have been examined, and daily concurrent administration at 6 mg/m² with standard radiation fractionation has also been used by some centers.107 There is no consensus on the optimal radiation fractionation regimen when combined with chemotherapy, and therefore standard fractionation is considered until further trials determine the role for altered fractionation.108,115 CRT has shown a benefit in advanced head and neck cancers in terms of survival, local/regional control, and larynx preservation over radiation-alone and IC regimens.117,121

The 2011 updated meta-analysis of chemotherapy in head and neck cancer (MACH-NC) included individual patient data from 2,767 patients with cancer of the hypopharynx, in addition to other head and neck tumor sites.116,122 For the entire population the addition of chemotherapy yielded an absolute overall survival benefit of 4.5% at 5 years (hazard ratio [HR] for death 0.88, 95% confidence interval [CI] 0.85–0.92). This benefit was only, however, observed in those managed with concurrent chemoradiotherapy and not for induction systemic therapy.116,122 While a similar survival benefit of chemotherapy was observed in the selected hypopharyngeal cancer patients (HR 0.88, 95% CI 0.80–0.96), no difference between IC versus concurrent chemoradiotherapy was identified, perhaps due to a lack of statistical power.116,122 Of note, the benefit of chemotherapy is age dependent, failing to meet statistical significance in the older than 71 age group. This cohort may thus be a particularly attractive population for treatment intensification with alternate radiation fractionation schemes.

14.12.2 Induction Chemotherapy and Sequential Chemoradiotherapy

Two limitations have plagued IC trials. First, the optimal chemotherapy regimen has been somewhat uncertain and thus non-uniform therapies are used across studies. Second, an initial focus on laryngeal malignancies has led to a comparatively less robust experience with hypopharyngeal carcinoma. An initial meta-analysis of three organ-preservation trials by Pignon et al, for example, identified only a single study focused on hypopharyngeal carcinoma.121 The EORTC phase III trial accrued pyriform sinus carcinomas (T2–T4, N0–N3), and identified no significant difference in overall survival (30 vs. 35%), or local (19 vs. 12%) and regional (23 vs. 17%) recurrence rates, between the IC and immediate surgery arms.123 A lower incidence of distant metastases in the IC arm (25 vs. 36%) was noted, but this did not translate into a survival benefit. The 5-year estimate of retaining a functioning larynx was 35%.123 While similar control and larynx preservation rates were identified in other series, the MACH-NC analysis has, however, alluded to the superiority of CRT over IC + radiotherapy.114,116,122,124,125

There continues, however, to be considerable interest in the optimization of IC, as it has the potential to be utilized for treatment selection. Those with responses to IC (e.g., > 50% decrease in tumor volume) being identified as most appropriate for a nonsurgical (radiotherapy vs. concurrent chemoradiotherapy) organ-preservation strategy.107,115 EORTC 24954, for example, randomly assigned advanced laryngeal/hypopharyngeal cancer patients with sequential (induction) chemotherapy + radiotherapy versus sequential (concurrent) chemoradiotherapy utilizing a cisplatin + 5-fluorouracil (PF) regimen.107,115,126 For those in the alternating arm not achieving at least substantial reduction in tumor bulk, immediate salvage surgery with adjuvant radiotherapy was undertaken. Similar acute/late toxicities were witnessed in both study arms with similar 3- and 5-year survival rates. There was a trend for improved laryngeal preservation in the IC group but this failed to reach statistical significance.107,115,126

To further enhance induction chemotherapy outcomes, a retrospective analysis of the TAX 324 trial demonstrated superiority of docetaxel, cisplatin, and 5-FU (TPF) over PF alone.127 The induction regimen in both arms was followed by concurrent chemoradiotherapy (utilizing weekly carboplatin). This study was not, however, designed to assess laryngeal preservation outcomes and combined early-/advanced-stage lesions, which limits the clinical applicability of these results.107,115 The phase II TREMPLIN larynx preservation trial compared of 153 stage III–IV laryngeal and hypopharyngeal carcinomas utilizing three
cycles of induction TPF. Those with a more than 50% (80%) response were further randomized to a platinum- versus Cetuximab-based concurrent chemoradiation therapy protocol. At the initial period of study analysis (18 months), high rates of laryngeal functional preservation (>80%) were achieved in those patients who were able to complete the treatment regimen. This, however, came with a high rate of grade III and IV toxicity, and two early deaths attributable to the induction regimen.79

Note
In some studies, induction chemotherapy has demonstrated a lower incidence of distant metastases (25 vs. 36%), however, these findings have not translated into a survival benefit.

14.12.3 Adjuvant Chemoradiation
Adjuvant chemoradiation involves the administration of concurrent chemothermy and radiation after definitive surgical resection. This strategy has been used for tumors considered to be at high risk of recurrence.113 A meta-analysis of four trials comparing postoperative radiation therapy alone with concurrent chemoradiation for stage III or IV cancers or early-stage cancers with high-risk pathologic features showed significant improvements in locoregional control and survival benefit in favor of chemoradiotherapy.114 Based on these results, postoperative concurrent chemoradiation should be considered for patients who have pathologic features suggestive of a high risk of recurrence (> Table 14.9) and who are able to tolerate the addition of chemotherapy.

The trade-off with concomitant chemoradiation is the increase in acute and long-term toxicity, including long-term dysphagia and G-tube dependence, irreversible side effects of chemotherapy such as nephropathy and neurotoxicity, and increased risk of postoperative complications after salvage surgery. Acute toxicity, such as severe mucositis or dysphagia, skin reaction, nausea and vomiting, weight loss, and hematologic toxicity can lead to interruptions and/or failure of completion of the full course of treatment. The toxicity carried with the treatment is not insignificant, and patients should be cared for at a center experienced with managing these toxicities. Patients must be involved in their treatment decision and informed of the benefits and drawbacks of organ-preservation treatment.

Note
Adjuvant concomitant chemoradiotherapy has shown a significant improvement in locoregional control and survival benefit, however, the trade-off with concomitant chemoradiation is the increase in acute and long-term toxicity.

14.13 Posttreatment Surveillance
Regular posttreatment follow-up is required to evaluate treatment response, detect early recurrence, and identify second primary tumors. Most local recurrences occur within 2 years of treatment, and early diagnosis is essential to initiate curative treatment.14,128,129 History, physical examination, endoscopic examination, and imaging techniques are important aspects of surveillance. Symptoms suggestive of recurrence include otalgia, odynophagia, dysphagia, and worsening neck pain. Suspicious findings on endoscopic examination include persistent edema in the region of the arytenoids, hypopharyngeal ulceration, and development of a fixed vocal cord. It is often difficult to differentiate persistent disease and recurrence from postoperative changes and inflammation associated with radiation therapy/chemoradiation, chondronecrosis of the laryngeal cartilages, or continued tobacco exposure in the postradiation setting.130,131,132 The risk of edema after radiation therapy is associated with total dose and field size and can persist for up to 18 months.128,133,134 Examination for regional recurrence can be similarly difficult due to changes in the neck such as fibrosis.

Diagnostic imaging should be obtained for routine assessment of response to treatment and in any patient with a suspicion of recurrence. The posttreatment diagnosis of local residual disease or recurrence may also be difficult to establish on a single CT or MRI scan, however, serial examinations are more reliable. PET/CT has proved to be particularly beneficial in this setting and has improved accuracy over CT and MRI.128,130,135 As part of routine surveillance, CT, MRI, and/or PET/CT scans should be obtained 3 months after treatment.130 A PET/CT scan performed at least 3 months after treatment is considered more specific, reducing false-positive scans that can result from active inflammation after treatment. A negative PET/CT scan reliably excludes residual or recurrent disease, whereas a positive scan necessitates a diligent search including endoscopy and biopsy. Regardless of PET or other imaging results, if there is strong clinical suspicion of persistent disease, biopsy is mandatory. Multiple endoscopies and biopsies may be needed to differentiate recurrence from posttreatment.

Note
Routine surveillance should include CT, MRI, and/or PET/CT scans obtained 3 months after treatment. A PET/CT scan performed at least 3 months after treatment is considered more specific, reducing false-positive scans that can result from active inflammation after treatment.

14.14 Treatment of Recurrence
14.14.1 Regional Recurrence
Complete response rates of cervical nodes to radiotherapy are reported to be between 59 and 83%. This is dependent on pre-treatment size, as poor response rates are achieved with nodes greater than 3 cm.137,138,139 Current evidence has suggested no benefit of planned neck dissection for advanced head and neck malignancies, instead favoring a posttreatment surveillance model.140 As described previously, imaging (e.g., PET/CT) should be considered at 3 months posttreatment to aid treatment planning. Patients with clinically or radiographically detectable incomplete responses (e.g., residual adenopathy ≥2-3 cm) should undergo a neck dissection for regional control.140,141 All other patients should continue active surveillance with regular...
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clinical examination (particularly for the first 2 years posttreatment) and symptom-/examination-guided imaging studies as necessary.142,143 Despite achieving regional control, survival is influenced by the high rate of distant metastases.49,141 Therefore, only a minority of patients subjected to the morbidity of a planned neck dissection will have a survival benefit.

14.14.2 Local and Distant Recurrence

The ideal treatment for locoregional treatment failure after organ preservation treatment protocols is surgical extirpation. However, most local recurrences present in a more advanced stage than the original primary, limiting the number of patients where salvage surgery is possible.144 Reirradiation with or without chemotherapy is one option to be considered in this setting. Long-term survivors have been reported utilizing this strategy for selected recurrent nasopharyngeal or laryngeal cancers, however, efficacy data for hypopharyngeal carcinomas are limited and derived from highly heterogeneous patient populations. For all patients treated with reirradiation, 5-year survival rates range from 13 to 93% (highly selected patients), and local control rates range from 12.5 to 42%, are reported. Severe or fatal complication rates may occur in 9 to 32% of patients.145 The addition of chemotherapy to reirradiation does marginally improve median survival but comes with a substantial increase in related toxicity.146 The treatment team must thus balance the risk of severe complications from these salvage approaches, while considering their detriment on quality of life, particularly given the relatively small possibility of long-term disease control.

Unresectable recurrent or metastatic disease has, however, traditionally been managed with chemotherapy, either for symptom palliation and/or achievement of a measurable reduction in tumor burden.137,147 Cisplatin + 5-FU-based regimen are traditionally used in this setting. Randomized trials have shown the equivalence of carboplatin + paclitaxel-based protocols, which are generally better tolerated with less acute toxicity.148 These conventional cytotoxic chemotherapy combinations have, however, had limited results with median survival ranging between 6 and 8 months and only rare long-term disease control beyond 2 years.148,149 The addition of cetuximab to these drug combinations, as demonstrated by the phase III EXTREME trial, can modestly improve median survival (10 months) with reasonable patient tolerance.150 Long-term outcomes are, however, unchanged with this approach. For patients with adequate performance status and organ function, clinical trial participation is thus an appropriate option to consider.

Given the limited treatment options for recurrent and/or metastatic head and neck cancers, the development of novel targeted agents in this population is of high priority. These agents exert their anticancer effects against specific proteins/pathways that are overexpressed or abnormally activated in malignant cells. Because of the high rates of epidermal growth factor receptor (EGFR) overexpression (80–90% of cases), this has been a prominent focus with both monoclonal antibodies (e.g., cetuximab) and small molecular tyrosine kinase inhibitors (e.g., erlotinib, gefitinib) utilized.151 Thus far, only cetuximab has generated significant tumor responses either in combination with conventional agents or as salvage for platinum-refractory cases.148,150 Afatinib (an ERBB family receptor blocker) has recently been employed as a second-line treatment for recurrent/metastatic cases, with a mild improvement in progression-free survival over conventional agents.152 Exploration of various potential molecular targets is thus ongoing in hopes of identifying an agent with significant antitumor activity against head and neck malignancies.

Note

Reirradiation provides an option for the management of recurrent disease with 5-year survival rates ranging from 13 to 93% and local control rates ranging from 12.5 to 42%. However, severe or fatal complication rates may occur in 9 to 32% of patients.

More recently immunotherapy has been shown to improve overall survival in patients with platinum refractory head and neck cancer.153 The main class of agent is the immune checkpoint inhibitors that target the programmed cell death protein 1 (PD-1) and its ligand (PD-L1) pathways. This pathway causes immunosuppression, and thus drugs that inhibit this interaction are able to induce antitumor T-cell responses. Data from trials testing nivolumab and pembrolizumab have shown favorable survival outcomes in the second-line setting and beyond. Trials testing these agents in combination with immune checkpoint inhibitors and/or in the first live setting are currently active and enrolling.154

14.15 Conclusion

Hypopharyngeal malignancies are uncommon and are particularly challenging to manage successfully. Low-risk disease (T1–T2 and N0–N1) can most often be controlled with a single modality (radiation vs. conservative surgical resection). Continued research is needed to determine with primary radiotherapy or transoral surgery should be considered ideal for early-stage disease. While published series of transoral surgery have yielded a high degree of local disease control and laryngeal preservation, these patients often require adjuvant radiotherapy. It is thus unclear which approach will have the lowest degree of acute and long-term treatment-associated morbidity.

Most patients will, however, present with advanced disease. In this setting, treatment planning must be highly individualized, balancing a desire for anatomical organ preservation with a clear goal of maintaining reasonable upper aerodigestive tract functioning. Despite intensive treatment protocols, there continues to be a high likelihood of treatment failure. Future research must endeavor to better integrate current management protocols with novel therapeutic strategies, to hopefully improve outcomes for our hypopharyngeal carcinoma patients.

14.16 Clinical Cases

14.16.1 Case 1: T2N2bM0 SCC Right Piriform Sinus

Presentation

This patient is a 63-year-old man with a 6-month history of right-side neck mass and some odynophagia. He has no history
of otalgia, dysphagia, or weight loss. He has a significant smoking and alcohol history. There was no history of significant medical comorbidity. Flexible endoscopic examination performed revealed a nodular lesion of the right piriform sinus, mobile cords bilaterally, and no pooling of secretions.

He was referred by his family physician to an otolaryngologist who performed a fine-needle aspiration of the right neck mass, which was positive for a poorly differentiated carcinoma. He was subsequently taken to the operating room for a panendoscopy. A complete direct endoscopic assessment was performed under general anesthesia, including flexible esophagoscopy, bronchoscopy, and laryngoscopy. Direct endoscopy revealed a nodular lesion of the right piriform sinus with extension to the lateral surface of the right aryepiglottic fold. There was no extension to the piriform apex or cervical esophagus. There was no evidence of a second primary lesion. Biopsy was obtained and confirmed to be a poorly differentiated SCC on final pathology. He was subsequently referred to a tertiary care oncology center.

**Diagnosis, Workup, and Staging**

CT scan of the head and neck with fine cuts through the larynx was performed (Fig. 14.8). Findings included thickening of the right piriform sinus and aryepiglottic fold. There was no cartilaginous or boney erosion, no invasion of the paraglottic space, or cervical esophageal extension. A right level III necrotic node was present measuring 2.1 cm and a 1.0 node in level II. Chest CT was also performed, which was negative. The tumor was staged as a T2N2bM0 SCC of the right piriform sinus.

**Options for Treatment**

The options for early carcinoma of the hypopharynx (T1–T2, N0–M0) include primary radiotherapy or surgery. Radiotherapy using conventional or altered fractionation can be used as a single-modality therapy with similar control and survival rates to surgery. The addition of chemotherapy may provide a marginal survival advantage and could be considered in this patient due to the advanced stage based on nodal disease, however, the additional morbidity must be anticipated.

Surgical options include transoral laser excision or standard partial pharyngectomy using a lateral pharyngotomy approach. Total laryngectomy is not indicated for early-stage lesions, except in selected cases not suitable for organ-preservation (surgical and nonsurgical) protocols. In centers with experience in laser surgery, this would be the optimal surgical approach for lesions limited to the lateral piriform sinus. Surgical excision would be made more difficult in this patient because of aryepiglottic fold involvement. For patients where the primary is managed surgically, the neck also needs to be treated using either neck dissection or postoperative radiotherapy. In patients with adverse pathologic features, postoperative radiotherapy would also be indicated.

**Treatment of the Primary Tumor and Neck**

The patient was discussed in a multidisciplinary tumor board conference, and both primary surgical and radiotherapy options were offered to the patient. The authors recommended to offer primary radiotherapy to both the primary site, both necks, and the paratracheal nodes. IGRT was performed to a dose of 70 Gy in 35 fractions. Radiation was chosen for this patient because of equivalent disease-related outcomes and minimal functional sequelae and also because of the probability of requiring adjuvant radiotherapy due to the likelihood of multiple nodal metastases. In this case, with the use of image-guided techniques, the tumor coverage is better than it would have been with conventional radiation, and the dose is reduced to one of the parotid glands, allowing preservation of saliva flow that would not be possible after conventional radiation therapy.

**14.16.2 Case 2: T4aN2aM0 SCC of the Piriform Sinus**

**Presentation**

This patient is a 60-year-old man with a 4-month history of progressive dysphagia associated with a 20-lb weight loss. His dysphagia was with both solids and liquids. Associated symptoms included odynophagia and right otalgia. He also noted a right-sided neck mass approximately 1 month prior to presentation that had slowly increased in size. He had a 40-pack-year smoking history and consumed two to three beers per day. There was no significant comorbidity history. On examination, he had mild stridor but did not appear to be in respiratory distress. He was thin and cachectic. Examinations of his oral cavity and oropharynx were normal. Otoscopic examination did not show any evidence of middle ear disease. Palpation of his right neck revealed a 3.5-cm level II or III node that was firm but not fixed. There were no palpable left neck masses. Flexible endoscopic examination found a large right-sided piriform sinus mass extending to involve the posterior pharyngeal wall. The right aryepiglottic fold appeared to be involved with reduction in the right vocal cord mobility.
CT scan showed a large exophytic mass filling the right piriform fossa with involvement of the right aryepiglottic fold, posterior pharyngeal wall, and left lateral piriform fossa. There was no extension to the cervical esophagus. Posteriorly, the mass abutted the prevertebral space with no evidence of invasion of the paraspinal muscles or cervical spine vertebrae. There was abnormal soft tissue around the lateral thyroid cartilage suggesting erosion. A 3.1-cm necrotic lymph node in right level III and a left retropharyngeal node measuring 1.5 cm were noted. Chest CT did not show any evidence of pulmonary metastases.

The patient was then taken to the operating room for panendoscopy and tracheotomy. Direct endoscopy confirmed CT scan and flexible laryngoscopy findings. The cervical esophagus appeared grossly normal on flexible esophagoscopy. There was no evidence of a synchronous primary tumor. A biopsy was performed, which confirmed a poorly differentiated SCC. The tumor was staged as T4aN2aM0. A G-tube was also placed percutaneously at the time of his admission.

**Diagnosis, Workup, and Staging**

CT scan showed a large exophytic mass filling the right piriform fossa with involvement of the right aryepiglottic fold, posterior pharyngeal wall, and left lateral piriform fossa. There was no extension to the cervical esophagus. Posteriorly, the mass abutted the prevertebral space with no evidence of invasion of the paraspinal muscles or cervical spine vertebrae. There was abnormal soft tissue around the lateral thyroid cartilage suggesting erosion. A 3.1-cm necrotic lymph node in right level III and a left retropharyngeal node measuring 1.5 cm were noted. Chest CT did not show any evidence of pulmonary metastases.

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**Treatment Options**

This patient requires combined-modality therapy with either the traditional approach of surgery and postoperative radiotherapy or an organ-preservation protocol with concurrent chemoradiation. Surgery would require a total laryngopharyngectomy with bilateral neck dissections and reconstruction with a free flap (jejunum or tubed fasciocutaneous flap). This patient requires discussion at a multidisciplinary tumor board conference, and both options need to be discussed with the patient. There is no comparative data to indicate which approach has superior disease-related or functional outcomes for this extent of disease. Either primary surgery or chemoradiation are reasonable approaches for extensive disease. Surgery would be recommended for T4 tumors with soft tissue extension because of the lower complication rate associated with primary surgery over salvage after chemoradiation. If surgery is performed, the patient is likely to require a flap (regional or free) reconstruction and adjuvant radiotherapy or chemoradiotherapy. Although chemoradiation may offer cure and larynx preservation for this patient, long-term functional outcomes are unpredictable given the pre-treatment functional status. Vocal cord fixation, marked dysphagia, and cartilage erosion are predictors of adverse outcome after chemoradiation. This patient is at high risk of distant metastases, which may be reduced by the addition of chemotherapy, however, there is no conclusive data to demonstrate an overall survival benefit.

**Treatment of the Primary Tumor and Neck**

The patient was assessed at a multidisciplinary tumor board and a recommendation of surgical therapy was made, however, this patient elected to undergo an organ-preservation approach with concurrent chemoradiation. Patients need extensive performance status workup prior to chemotherapy including assessment of hematologic, liver, and renal function. The concurrent chemoradiation regimen given was 100 mg/m² cisplatin for three cycles on days 1, 22, and 43 with standard fractionation radiotherapy (70 Gy in 2 Gy per fraction over 7 weeks).

The nodal disease was managed with bilateral irradiation. Clinically, this patient had a complete response, however, on a follow-up PET/CT scan at 3 months, there was persistent uptake in the ipsilateral neck consistent with persistent nodal disease. There was no uptake at the primary site. A fine-needle aspiration was suspicious for persistent nodal disease. A salvage neck dissection was recommended. A direct endoscopy was performed prior to the neck dissection to assess the response at the primary site. Examination showed a complete response and frozen-section analysis of biopsies from the primary site were negative, therefore we proceeded with a modified radical neck dissection performed with preservation of the accessory nerve. Final pathology found metastatic SCC in 4 of 52 lymph nodes. Although his tracheotomy was able to be decannulated, his
vocal function was impaired and he was able to maintain a soft diet only.

14.16.3 Case 3: Recurrent T4N0M0 Postcricoid Carcinoma after Concurrent Chemoradiation

Presentation
This third patient is a 62-year-old man who was treated in 2003 for a T3N2bM0 postcricoid SCC with concurrent chemoradiation. He required a G-tube and tracheotomy during treatment and was unable to be decannulated or have the G-tube removed after the completion of treatment. Approximately 6 months after treatment, he developed progressive odynophagia. On flexible endoscopy, persistent edema and ulceration of the postcricoid region were noted. Vocal cord mobility was severely limited bilaterally. Neck examination was difficult because of fibrosis.

Diagnosis and Workup
A PET/CT scan was obtained, which revealed uptake at the primary site and neck. CT scan of the neck showed soft tissue thickening in the postcricoid region extending to the inferior aspect of the cricoid. Direct endoscopy was performed under general anesthesia confirming the findings seen on flexible examination. There was no extension of the lesion to the cervical esophagus. Biopsy of the ulcer was obtained, and frozen section confirmed recurrent SCC. Based on the imaging and endoscopy, the recurrent disease was deemed to be resectable.

Treatment Options
Surgical salvage, where possible, is the preferred modality for managing recurrent hypopharyngeal cancer. Reirradiation with or without chemotherapy is associated with significant morbidity and was not recommended for this patient. The main clinical decision for this patient is the best method of reconstruction, which will depend on the extent of resection and previous therapy (radiation with or without chemotherapy). Options for reconstruction of a circumferential laryngopharyngeal defect without esophagectomy include regional and free tissue flaps. The most widely used regional flap is the pectoralis major flap, however, the authors would not recommend this reconstruction due to the difficulty tubing this flap and the poor functional outcome. Free flap options include either fasciocutaneous or enteric flaps. The anterolateral thigh is our preferred fasciocutaneous flap reconstruction because of the low donor-site morbidity and fistula rate. The most widely used enteric flap is free jejunum, however, authors’ preference for these high-risk reconstructions is the gastro-omental free flap. Patients who have undergone prior chemoradiation are at high risk of fistula, wound complications, and potential major vessel rupture. The gastro-omental flap has the advantage of highly vascular omentum to wrap around the pharyngeal anastomoses and major vessels, and we believe that the speech and swallowing outcomes are superior to jejunum.

Treatment of the Primary Tumor and Neck
Referral was made to a speech therapist to discuss voice rehabilitation, and the patient was in agreement with the management plan. A total laryngopharyngectomy was performed along with bilateral level II to IV neck dissections for potential occult disease and vessel preparation (Fig. 14.10). A gastro-omental flap (Fig. 14.11, Fig. 14.12, Fig. 14.13) was chosen for reconstruction because of the poor wound-healing abilities of chemoradiated tissue. The patient recovered without any complications, and a secondary TEP was performed at a later date.
Fig. 14.11 Case 3: Gastro-omental flap is being harvested. The greater curvature and omentum are taken. A chest tube is placed through the stomach, and a gastrointestinal anastomosis (GIA) stapler is then used to divide the stomach above the chest tube.

Fig. 14.12 Inset of the gastro-omental flap into the total laryngopharyngectomy defect.
Fig. 14.13 Cephalic-mental free flap inset with omentum draped over
the flap and the neck providing coverage of the carotid arteries and left
internal jugular vein.

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Carcinoma of the Hypopharynx


15 Carcinoma of the Larynx

Moustafa W. Mourad, Sami P. Moubayed, and Raymond L. Chai

15.1 Epidemiology

Currently new laryngeal cancer rates occur at a rate of 3.2 new cases per 100,000 men and women per year with a lifetime risk of 0.4% for developing cancer.1,2 The majority of individuals diagnosed with cancer of the larynx are older than 50, with an overall declining incidence.3,4 The recent decline in the incidence of laryngeal cancer has been attributed to the declining rates of smoking among younger populations as well as evolving tobacco-related legislation and marketing.5,6,7 Approximately 95% of all laryngeal cancers are squamous cell carcinoma (SCC), which is the primary focus of this chapter.8,9

Note

The incidence of tobacco-related laryngeal cancer is on the decline.

15.2 Etiology

The primary etiologic factor for the development of laryngeal cancer is chronic tobacco use. The lifetime risk increases with increased exposure.4,5 Other etiologic factors have been implicated in the pathogenesis of laryngeal cancer including gastric reflux and concomitant human papillomavirus (HPV) infection, although their etiologic role has not been completely defined.10,11,12 The role of HPV infectivity has been better defined in prognostication of other head and neck sites such as the oropharynx, with less impact for the larynx.13,14

15.3 Anatomy of the Larynx

Understanding the complex three-dimensional anatomy of the larynx is imperative for directing appropriate treatment.10,15,16 The larynx extends from the tip of the epiglottis to the inferior border of the cricoid and is comprised of three nonpaired cartilages (epiglottis, thyroid cartilage, cricoid cartilage) and three paired cartilages (arytenoid, cuneiform, corniculate). The larynx is further subdivided into specific anatomical spaces including the preepiglottic, paraglottic, and subglottic spaces that impact tumor growth and spread (Fig. 15.1). The preepiglottic space is bounded by the thyrohyoid membrane and thyroid cartilage anteriorly, vallecula and hyoid superiorly, the superior aspect of the paraglottic spaces posterolaterally, and the epiglottis posteriorly. The preepiglottic space contains a rich matrix of vasculature and lymphatic vessels that allows for early tumor spread; invasion has a negative impact on oncologic outcomes.15,17,18 Furthermore, extent of involvement of the preepiglottic space is important as tumor may extend to the arytenoid, aryepiglottic folds, ventricle, base of tongue, or the superior medial aspect of the pyriform sinus, having implications in directing management options.
The paraglottic space was first described by Tucker and Smith, bounded by the quadrangular membrane superiorly and medi-
ally, the conus elasticus inferiorly and medially, the thyroid carti-
lage anterolaterally, and the piriform sinus posteriorly.19,20 The
paraglottic space is a compartment that contains the ventricle,
saccule, and thyroarytenoid musculature. The paraglottic space is
important as it facilitates communication and spread of tumor
between the supraglottis as well as the subglottis, in addition to
being intricately associated with the pyriform sinuses. Further-
more, this space provides a low-resistance pathway for the direct
extension of laryngeal cancer inferiorly and superiorly.21,22

The subglottic region extends from a plane 1 cm below the
true vocal cords to the lower edge of the cricoid cartilage. Pri-
mary or secondary involvement of the subglottis has been con-
sidered to be a poor prognostic indicator due to the low
impedance for direct extralaryngeal extension between tra-
cheal rings, the rich network of vascular and lymphatic vessels,
and potentiating superior extension through direct communi-
cation with the paraglottic space.10,19,21,23,24

The paraglottic space is a compartment that contains the ventricle,
saccule, and thyroarytenoid musculature. The paraglottic space is
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cheal rings, the rich network of vascular and lymphatic vessels,
and potentiating superior extension through direct communi-
cation with the paraglottic space.10,19,21,23,24

Two major nerve branches, the superior laryngeal nerve (SLN)
and the recurrent laryngeal nerve (RLN), supply motor function
and sensation to the larynx. Both branches arise from the vagus
nerve. The SLN arises from the inferior ganglia joining with cervi-
cal sympathetic fibers that ultimately divide into an external and
internal branch. The external branch of the SLN is a motor
branch that provides motor input to the cricothyroid muscle. The
internal branch of the SLN pierces through the thyrohyoid mem-
brane providing sensory innervation from the supraglottis to the
level of the glottis. The RLN courses in the tracheoesophageal
groove, providing motor innervation to all intrinsic musculature
(with the exception of the cricothyroid) of the larynx, in addition
to providing sensory innervation to the subglottic region.
15.4 Staging

Laryngeal cancer is currently staged based on the American Joint Committee on Cancer (AJCC) TNM staging system. Complete staging of laryngeal tumors is comprised of histopathology, physical examination, endoscopic and radiologic mapping, in addition to metastatic workup. Tumor staging (T) is based on tumor characteristics related to subsite involvement, tumor extension, and degree of vocal fold mobility. Nodal staging (N) is related to size, number, and laterality of involved nodes, while metastatic staging (M) is determined by the presence of distant disease.

In staging supraglottic lesions, T1 lesions are defined as those only involving one subsite, T2 cancers involve multiple subsites or extension to the glottis or subglottis, and T3 lesions involve extension into the paraglottic or preepiglottic spaces or minor involvement of the thyroid cartilage. T4 lesions are defined as those lesions that have locally advanced disease with full-thickness involvement of the thyroid cartilage or extension into the oropharynx. Glottic T1 lesions have limited involvement of one vocal fold (T1a), or both vocal folds with no impact on mobility (T1b). T2 lesions extend into the supraglottis or subglottis or have impaired vocal fold mobility. T3 lesions either involve the paraglottic space or have vocal fold fixation. Finally, T4 lesions have locally advanced disease with cartilage invasion or extralaryngeal spread. Primary subglottic lesions are T1 if they are limited to the subglottis, T2 if there is superior extension involving the glottis with no impact on mobility, and T3 if the vocal fold is fixed. T4 lesions are those locally advanced lesions with involvement of the cricoid cartilage, thyroid cartilage, or involvement of extralaryngeal structures. Nodal staging (N) is similar for all subsites and consistent for all laryngeal tumors. Metastatic disease is based on the presence (M1) or absence (M0) of distant disease (Table 15.1, Table 15.2).

15.5 Presentation

The three primary functions of the larynx include phonatory, respiratory, and protective mechanisms. Presentation of tumors in this region may compromise either one or a combination of these functions. Symptoms are highly dependent on the size of the tumor, location, and patient-related factors. Common complaints include dysphonia, dysphagia, dyspnea, or hemoptysis. Furthermore, compromise to the aerodigestive conduit may result in poor oral intake and subsequent weight loss and malnutrition, as well as aspiration and/or pneumonia. Asymptomatic lesions, particularly in the supraglottis and subglottis, may also present as a neck mass. Finally, supraglottic lesions may present with referred ear pain or odynophagia due to vagus nerve involvement.

Table 15.1 TNM tumor staging system of laryngeal cancer by subsite: larynx

<table>
<thead>
<tr>
<th>subsite</th>
<th>staging system</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to one subsite of the supraglottis with normal vocal fold mobility</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades mucosa of more than one adjacent subsite of the supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to the larynx with vocal fold fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or inner cortex of thyroid cartilage</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>subsite</th>
<th>staging system</th>
</tr>
</thead>
<tbody>
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<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the vocal fold(s) (may involve anterior posterior commissure) with normal mobility</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor limited to one vocal fold</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor involves both vocal folds</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to the supraglottis and/or subglottis, and/or with impaired vocal fold mobility</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to the larynx with vocal fold fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease. Tumor invades the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
</tr>
</tbody>
</table>

Note

Common complaints associated with glottis carcinoma include dysphonia, dysphagia, dyspnea, or hemoptysis. The presenting signs and symptoms are largely dependent on the location of the tumor in the extent of the lesion.
### Table 15.1 (Continued) TNM tumor staging system of laryngeal cancer by subsite: larynx

<table>
<thead>
<tr>
<th>c. Primary tumor (T) subglottic larynx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the subglottis</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to the vocal cord(s) with normal or impaired mobility</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to the larynx with vocal fold fixation</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
</tr>
</tbody>
</table>

Note: The larynx includes all laryngeal structures from the tip of the epiglottis to the cricoid cartilage interiorly and is subdivided into three specific sites: supraglottis, glottis, and subglottis.

### Table 15.2 Final staging of tumor based on TNM criteria: larynx

<table>
<thead>
<tr>
<th>a. Regional lymph nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node &gt;1 cm but not &gt;6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none &gt;6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none &gt;6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node &gt;3 cm but not &gt;6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none &gt;6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none &gt;6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt;6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. Distant metastasis classification (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>c. Stage grouping</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>T1, N1, M0</td>
<td></td>
</tr>
<tr>
<td>T2, N1, M0</td>
<td></td>
</tr>
<tr>
<td>T3, N1, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a, N0, M0</td>
</tr>
<tr>
<td>T4a, N1, M0</td>
<td></td>
</tr>
<tr>
<td>T1, N2, M0</td>
<td></td>
</tr>
<tr>
<td>T2, N2, M0</td>
<td></td>
</tr>
<tr>
<td>T3, N2, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td>T4b, Any N, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV C</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>
15.6 Diagnosis and Workup

Initial diagnosis and workup of laryngeal lesions begin with a basic history and physical examination. The history should include the nature of the patient’s dominant complaints, smoking status, prior surgeries, and comorbidities. Clinicians should have a low index of suspicion and a lower threshold for workup of high-risk patients (i.e., heavy tobacco users) with a history of hemoptysis, long-standing dysphonia, neck masses, odynophagia, or unilateral otalgia in the absence of obvious pathology. The most recent 2009 clinical practice guidelines indicate that visualization of the larynx should be performed in the setting of hoarseness for 3 months that has failed to resolve, or if serious underlying etiology is suspected.3,27

The most recent 2009 clinical practice guidelines indicate that visualization of the larynx should be performed in the setting of hoarseness for 3 months that has failed to resolve, or if serious underlying etiology is suspected.3,27

Visualiation mapping of laryngeal lesions should include specific attention to vocal cord mobility, airway patency, and extent of tumor spread. Clinicians should note the relationship of lesions to specific subsites of the supraglottis, glottis, and subglottis. Involvement of the aryepiglottic folds, postcricoid region, arytenoid processes, valleculae, and subglottis are particularly important as they may guide treatment options and have impact on staging. Furthermore, adjacent spread to the piriform sinuses, base of tongue, and pharyngeal wall should be evaluated. Biopsy should be pursued in the presence of any laryngeal lesions.

Adjuvant workup studies of laryngeal lesions are guided by subsite involvement and extent of lesion spread. Because of significant tobacco history in the majority of patients, consideration for chest radiography should be performed. Thin-cut computed tomography (CT) with contrast through the neck and/or magnetic resonance imaging (MRI) to detect radiographically positive lymphadenopathy as well as facilitate submucosal and cartilaginous mapping of tumors should be performed. Special attention should be given to involvement of the preepiglottic and paraglottic spaces, as well as that of the cricoid and thyroid cartilages.10,35 Furthermore, because of the clinically significant rate of distant spread in stages III-IV tumors, further workup using positron emission tomography (PET)/CT should be considered.13,36 When conservation laryngeal surgery is considered, pulmonary reserve can be quantified using pulmonary function tests to determine if patients may be candidates for such procedures.

15.7 Regional Disease

Rate of advanced locoregional disease is highly subsite dependent, and more likely to occur in lesions of the supraglottis and subglottis.15,16,17 High rates of regional disease can be attributed to rich lymphatic networks of the supraglottis that drain bilaterally, resulting in occult nodal metastases regardless of T stage in up to 75% of cases, with bilateral involvement in 18 to 26% of cases.15,18,38 Similarly, subglottic lesions have little impedance to extralaryngeal spread due to the absence of a strong fibroelastic barrier in the region. Strome et al found on examination of chondroid tissue that direct extension of tumor occurred through gaps in the tracheal cartilage, with little erosive changes to the cartilaginous framework.19,31 Similarly, a rich lymphatic drainage network in the region allows for nodal spread through the cricothyroid membrane and the cricothyroid membrane resulting in anterior and posterolateral nodal involvement, respectively.21,39
Carcinoma of the Larynx

Note
Subglottic lesions have little impedance to extralaryngeal spread due to the absence of a strong fibroelastic barrier in the region. As a result of direct extension, metastatic disease is not uncommon in subglottic tumors.

Glottic cancers, however, have lower rates of regional metastasis due to the strong fibroelastic framework of the larynx that prevents extralaryngeal spread. Rates of regional metastases in early-stage cancers have been reported as low as 0%, with T3 and T4 lesions having reported rates between 20% and 30%.27,28,41

15.7.1 Treatment

Treatment of laryngeal cancer remains highly controversial with current research efforts focused on defining the role of nonsurgical and surgical interventions. The landmark study by the VA Laryngeal Cancer Study group demonstrated equal efficacy of nonsurgical and surgical interventions in the treatment of advanced-stage laryngeal cancer, with no clear survival benefit to either treatment arm.27,33 Such studies have established the role of organ preservation protocols in the treatment of laryngeal cancer. Since the 1991 VA study, institutions have expanded their efforts to determine the role of induction chemotherapy and concurrent therapy to better determine optimal treatment strategies, with no clear consensus approach emerging.27,28,30 Optimal treatment strategies are thought to be heavily influenced on tumor volume and perceived chemosensitivity/radiosensitivity. Furthermore, advancement in minimally invasive technologies has ushered in a new era of surgical management of laryngeal tumors and organ preservation.31,32,42

Surgical Treatment

A wide array of surgical treatments exists for the management of laryngeal cancers, with treatment strategies guided by stage and site of involvement. Surgical options can broadly be grouped into function- and non-function-preserving procedures. Function preservation surgeries can be further subdivided into open transcervical approaches and minimally invasive transoral approaches.

Laryngeal Function Preservation Therapy: Minimally Invasive Transoral Techniques

Recent advancements in technology have led to the development of minimally invasive transoral techniques including transoral robotic surgery (TORS) and transoral laser microsurgery (TLM). Indications for transoral resections include the same criteria set by Biller et al for open surgery (Table 15.3) in addition to the ability to expose and visualize the entirety of the lesion through direct laryngoscopy.10,28,34 In the late 1980s, Steiner et al developed TLM for the treatment of aerodigestive tract tumors utilizing direct laryngoscopy, the operating microscope, microsurgical instruments, and the CO2 laser to perform piecemeal resection.10,35 Widespread acceptance of the technique led to increased usage in early-stage glottis, supraglottic, oropharyngeal, and hypopharyngeal lesions.10,36 In a multicenter study of TLM outcomes for stages I to III cancers of the larynx by Agrawal et al, 3-year overall and disease-free survival rates were reported to be 88% and 79%, respectively.43 However, the technical expertise required has hindered widespread acceptance of TLM.38,44,45 Furthermore, TLM has been criticized due to the inability to remove tumors en bloc and the requirement for piecemeal resection. In inexperienced hands, this may compromise assessment of the tumor margin and result in understaging of the primary tumor.27,28 The use of TORS, particularly for endoscopic supraglottic laryngectomies, may allow for improved confidence on surgical margins since tumors are removed en bloc (Fig. 15.5).

Currently, TLM is indicated for T1, T2, and select T3 supraglottic cancers.39,46 The technique by which TLM is performed is highly variable and depends on tumor extent. This ranges from cordectomies (types I–V) to partial supraglottic resections to partial laryngectomies. TLM typically employs the CO2 laser deployed through direct visualization via suspension microlaryngoscopy. Tumors are removed in piecemeal and reoriented after resection and assessed by the pathologist to clear the margin.

Laryngeal Function Preservation Surgery: Open Transcervical Techniques

Function preservation surgery was first introduced in 1963 by Piquet et al in an attempt to ameliorate the detrimental impact of total laryngectomy.45,46 There was a resurgence in worldwide interest in these procedures in the mid-1990s.41,48 Indications for function preservation surgery were set forth by Biller et al ensuring sound oncologic resection with the ability to achieve margins without compromising functional or structural integrity of the larynx (Table 15.3).21,49 Although variations of the originally described procedures exist, these surgeries are defined by the extent of resection involved in addition to the method of reconstruction.10,28 Broadly defined, partial laryngectomy surgeries can be grouped as either vertical partial laryngectomies (VPL) or horizontal partial laryngectomies (HPL).

Table 15.3 Indications for transoral resections set forth by Biller et al for partial laryngeal surgery

<table>
<thead>
<tr>
<th>Indications for transoral resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor extension to the contralateral cord should be no greater than 3 mm</td>
</tr>
<tr>
<td>The arytenoid process (save for the vocal process) should be free of disease</td>
</tr>
<tr>
<td>There should be limited subglottic extension not &gt; 5 mm</td>
</tr>
<tr>
<td>Supraglottic extension should be no greater than the lateral extension of the sinus of Morgagni</td>
</tr>
<tr>
<td>The remaining vocal cords should be mobile</td>
</tr>
<tr>
<td>Cartilaginous extension should be absent</td>
</tr>
</tbody>
</table>

Note

The indications for laryngeal conservation surgery are based on the tenets of ensuring sound oncologic resection with the ability to achieve oncologic margins without compromising functional or structural integrity of the larynx.
Vertical partial laryngectomies facilitate access to the glottic level via a vertical median or paramedian thyroid cartilage incision. This allows for visualization of the entire endolarynx, providing access to the glottis, supraglottis, and subglottic levels. Excision of the tumor is performed en bloc, with direct ability to obtain tissue for margin analysis. VPL is indicated in large T1 lesions, small T2 lesions with minimal supraglottic and subglottic extension, early lesions not amenable to transoral resection due to inadequate visualization, and in early-stage recurrent salvage.

Horizontal partial laryngectomies involve a horizontal incision through or above the thyroid cartilage to gain access to glottic, transglottic, and supraglottic lesions. Depending on the site of entrance into the endolarynx, level of resection, and method of reconstruction, HPL can be defined as (1) supraglottic partial laryngectomy (SPL), (2) supracricoid laryngectomy with cricohyoidoepiglottopexy (SCL-CHEP), and (3) supracricoid laryngectomy with cricohyoidopexy (SCL-CHP). Surgery is guided by the principle of en bloc resection of units of the larynx (as opposed to simply excising tumor) that may include resection of normal tissue in order to enhance the reconstruction to preserve functional integrity. Depending on the tumor extent, such units may include all endolaryngeal structures superior to the cricoid (SCL) or structures superior to the glottis (SPL; Fig. 15.6). Reconstruction is performed by securing the cricoid to the epiglottis (CHEP) if preserved, or to the hyoid (CHP). Indications for these procedures include (1) early-stage T1–T2 glottic, supraglottic, or transglottic cancers; (2) select T3 glottic, supraglottic, or transglottic cancers; and (3) select T4 lesions with minor thyroid cartilage involvement alone that spare the outer perichondrium. Three-year and 5-year overall survival rates for function preservation surgeries range from 71 to 95% and 79 to 88%, respectively.

Non–Function-Preservation Laryngeal Surgery: Total Laryngectomy

Surgical removal of the entire larynx from the epiglottis to the subglottis is referred to as total laryngectomy. Because of advanced disease, oftentimes this may involve removal of all or part of the pharynx, referred to as a total laryngopharyngectomy. Because of the associated morbidity and social stigma associated with total laryngectomy, studies have attempted to define the indications and role of surgery compared to organ preservation options. In the 1991 VA study, organ preservation occurred at rate of 64% in advanced-stage lesions treated with induction chemotherapy and radiotherapy without compromise to survival benefit when compared to surgery. A similar study by the European Organization for Research and Treatment of Cancer (EORTC) found equivalent survival for organ preservation and non–organ-preservation
Treatment modalities.46,60 The study, however, assessed outcomes in hypopharyngeal cancers requiring total laryngectomy and not localized laryngeal lesions. Optimum treatment strategies, however, continued to remain controversial with other studies showing contradictory improvement in surgery plus adjuvant radiation groups when compared to primary chemoradiation groups.47,61 Other studies explored the role of induction chemotherapy in the treatment of advanced-stage cancers. Beauvillain et al showed improved locoregional control and overall survival in patients receiving induction therapy in addition to surgery and radiation, as opposed to induction chemotherapy and radiation therapy alone.50,62 Their study demonstrated superior outcomes with the addition of surgery as opposed to organ preservation with induction chemotherapy.

More recently, however, Megwalu and Sikora performed a population-based study on more than 5,000 patients, demonstrating a statistically significant improvement in overall and disease-specific survival in patients receiving surgical therapy as opposed to nonsurgical management modality.46,63 In a similar population study of the National Cancer Database by Hoffman et al in 2006, they also found decreased survival in patients with laryngeal cancer in the mid-1990s corresponding with the overall paradigm shift to organ preservation modalities. Most notably they determined a decline in 5-year survival in patients with T3N0M0 disease receiving organ preservation treatment when compared with therapy that employed surgery.64

**Note**

Recent data suggest that there is a decline in 5-year survival in patients with T3N0M0 disease receiving organ preservation treatment when compared with therapy that employed surgery.

The Radiation Therapy Oncology Group (RTOG) 91–11 study compared concurrent chemoradiation to induction chemotherapeutic options. The study found improved laryngeal preservation rates in concurrently treated patients when compared to induction chemotherapy or primary radiation groups. This study, however, was limited to stage III cancers, excluding T4 lesions that were likely to have compromised organ preservation outcomes from the outset.28,65 Despite the lack of clear consensus with regard to the best treatment options for advanced-stage disease of the larynx, total laryngectomy remains an important surgery in the armamentarium of management options (+ Fig. 15.9). Total laryngectomy plays an important role in the management of primary T4 cancers of the larynx, patients presenting with a dysfunctional larynx who would otherwise be considered good candidates for organ preservation, and patients for whom swallowing function is more important than voice outcomes. Furthermore, total laryngectomy is the gold standard in the salvage setting with only a select group of early-stage lesions being amenable to partial laryngeal surgery.50,51,66

**Note**

Total laryngectomy plays an important role in the management of primary T4 cancers of the larynx. Such patients often present with a dysfunctional larynx that will not improve following therapy.

### 15.7.2 Nonsurgical Treatment

**Radiation**

Radiation therapy plays an important role in the treatment of early-stage lesions of the glottis. T1 lesions can be treated with a total of 63 to 70 Gy, depending on the dosing schedule. Studies have shown that a minimum of 2.25 Gy per day is superior to 2 Gy per day and can reduce overall dose to 63 Gy, but with a potential increase in late-term toxicity.52 T2 lesions are treated similarly with an increase in field coverage due to a slightly
increased risk of regional disease, particularly to the pretracheal and paratracheal lymph nodes. The optimal treatment of early-stage laryngeal cancers, however, remains elusive. Both surgery and radiotherapy have excellent local control and overall survival. However, failure in the setting of primary radiotherapy may be detrimental due to the preclusion of further radiation therapy in the salvage setting. Mourad et al found that treatment of early-stage lesions was influenced by region, socioeconomic status, and race. They also determined that overall survival was improved in patients receiving radiation therapy. However, in a study by Brady et al, an overall improvement in 5-year disease-free survival was observed in T1 disease treated with surgery when compared to radiation. This same improvement in survival, however, was not observed in T2 lesions. They therefore advocate for surgery as first-line therapy in T1 lesions.

Radiation monotherapy for advanced glottic lesions is also a consideration. In the RTOG 91-11 study, the radiation monotherapy arm had a similar overall survival to the two arms receiving chemotherapy. However, the 10-year follow-up suggested a decrease in overall survival for concurrent chemoradiotherapy (CRT) patients, possibly related to treatment-related toxicity when compared to RT alone. Therefore, radiation monotherapy can be administered to late-stage tumors in patients who are poor candidates for either surgery or chemotherapy. Radiation therapy also plays a pivotal role in the adjuvant setting for advanced-stage lesions. Whether organ preservation or non–organ-preservation modalities are pursued, radiation is an important adjunct to overall treatment strategies. In the postoperative setting, poor prognostic correlates including involvement of two or more nodes, extracapsular extension, close or positive resection margin, perineural invasion, large tumor bulk, and lymphovascular invasion may warrant adjuvant radiation therapy. Postoperative tumor dosing usually requires a total of 60 to 66 Gy over a 6-week period.

Nonsurgical treatment of subglottic cancer as a primary treatment modality is, however, more limited owing to the higher degree of invasiveness, propensity for lymphovascular and
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Regional spread, in addition to overall worse prognosis. Primary subglottic carcinoma is much rarer than other laryngeal tumors, but the majority of published studies advocate combined surgical and radiation therapy, even in cases of early-stage lesions. In a study by Dahm et al of early-stage subglottic cancers, cancers treated with radiation monotherapy had a statistically significant reduced disease-free survival (22%) when compared to surgical groups (42%), or bimodality surgery plus adjuvant radiation reduced disease-free survival (22%) when compared to surgical groups treated with radiation monotherapy had a statistically significant

Santoro et al studied advanced-stage subglottic cancer, and found overall 5-year survival was 0% in patients treated with radiotherapy alone, compared to 47% in surgical groups, and 83% in combination treatment groups. The role of nonsurgical management of supraglottic cancer also remains controversial. Sessions et al studied different treatment protocols for supraglottic cancer in more than 600 patients, finding no survival benefit for any given treatment approach. However, they found improved laryngeal preservation rates in patients receiving supraglottic laryngectomies. Jones et al studied early-stage supraglottic cancer patients receiving surgery or radiation, finding no survival advantage to either modality. However, patients receiving surgery alone did not receive staging or elective neck dissections at the time of tumor removal. Spriano et al, however, did find improved oncologic outcomes in those patients receiving surgery when compared to radiation groups, in addition to improved function preservation. Most recently, a population-based study by Arshad et al found that patients receiving organ preservation surgery in addition to neck dissection for early-stage supraglottic cancer had improved survival when compared to patients who received radiation therapy alone. Because nonsurgical therapy of the supraglottic carcinoma requires radiotherapy fields that include the primary site and bilateral necks (*Fig. 15.10), the radiation volumes can result in pharyngeal fibrosis and long-term dysphagia.

Chemotherapy

Chemotherapy is used in the treatment of advanced-stage lesions for improved locoregional control in addition to systemic control. In 1985, Hong et al found that chemoresponsive laryngeal tumors predicted radiosensitivity, which formulated the basis for the VA laryngeal cancer study. The VA laryngeal cancer study group demonstrated equal efficacy of nonsurgical chemotherapy-based treatment options to surgical interventions in the treatment of advanced-stage laryngeal cancer when treatment was guided based on tumor responsiveness to chemotherapy. The RTOG 91–11 study demonstrated improved laryngeal preservation in patients receiving concomitant chemotherapy when compared to induction therapy. In addition, biological agents such as cetuximab have shown efficacy when combined with radiation therapy and are thought to enhance radiosensitivity through blockage of the epidermal growth factor receptor (EGFR) pathway.

Hong’s study in 1985 also set the precedent for administration of chemotherapy to determine subsequent treatment. A Phase II clinical trial from the University of Michigan demonstrated that single-cycle induction chemotherapy responsiveness (50% or greater) was strongly predictive of radiosensitivity. Improved patient selection for organ preservation modalities resulted in an overall 85% survival at 3 years and 70% preservation of the larynx. Nonresponsive tumors were thought to be radioresistant and managed with surgical options.

**Note**

The RTOG 91–11 study demonstrated improved laryngeal preservation in patients receiving concomitant chemotherapy when compared to induction therapy.

Large phase III clinical trials by the RTOG and EORTC have supported the use of adjuvant chemotherapy in the postoperative period. The benefit of adjuvant chemotherapy was found primarily in patients with extracapsular extension or positive surgical margins.

15.8 Management of the Neck

The predicted nodal basins for metastases from laryngeal malignancies are levels II to IV, and involvement portends a worse prognosis. Typically patients with N1 disease can be managed with single-modality therapy. RTOG 91–11 patients with N2 disease received staged neck dissections 8 weeks after completion of radiation therapy as a means of bimodality therapy. However, since the advent of the PET scan, some authors advocate for posttreatment scans with surgical intervention only for patients demonstrating hypermetabolic activity. Recently, a study by Mehanna et al demonstrated similar survival in patients undergoing neck dissection when compared to PET/CT surveillance for advanced head and neck cancer. PET/CT surveillance, however, was associated with lower costs. Their study, however, consisted mostly of oropharyngeal cancer (84%), the majority of which were HPV positive (75%). However, the sensitivity of such scans has been called into questions in studies demonstrating occult residual disease in negative
Controversy exists in the treatment of the N0 neck. Options include observation and elective neck intervention. Elective neck interventions are divided into surgical (neck dissection) and nonsurgical (radiotherapy) interventions. The type of elective neck intervention may be impacted by the treatment of the primary tumor. Tumors treated primarily with radiotherapy may be better suited with including the neck in the radiation field. Surgical elective interventions, however, may provide valuable pathologic information that could guide adjuvant therapy.

**Note**
There is no consensus on management of the N0 neck, however, the tumor subsite should play a key role in guiding treatment of the N0 neck.

Early-stage glottic cancers have a low rate of occult metastases, with observation being a viable option, particularly when treated with endoscopic resection. Late-stage lesions of the glottis, however, may benefit from therapeutic intervention to the neck. Supraglottic lesions that are T2 or greater have a higher rate of occult metastases (>20%) and intervention in the N0 neck may be warranted. Furthermore, the rate of bilateral metastases is 18 to 26%, warranting bilateral intervention.

### 15.9 Clinical Cases

#### 15.9.1 Case 1: T3N0M0 Glottic Cancer

**Presentation**
The patient is a 49-year-old man with a 30 pack-year smoking history who presents with a 7-month history of hoarseness. He currently is a telemarketer whose job requires him to speak all day. He denies any associated dysphagia, odynophagia, or otalgia.

**Physical Examination**
Examination is remarkable for left-sided exophytic mass along the true vocal cord. The cord is fixed, but arytenoid seems to be mobile. Palpation of the neck reveals no clinically evident nodes.

**Diagnosis and Workup**
The patient undergoes direct laryngoscopy with biopsy. Examination under anesthesia reveals no anterior commissure involvement, with the tumor extending to the left vocal process. There is no extension grossly visible into the supraglottic region. Examination of the subglottis reveals no inferior extension of the tumor. CT neck with contrast reveals no radiologically positive nodes or cartilaginous involvement but demonstrates a lesion with left paraglottic space involvement (Fig. 15.11). Patient also had a chest X-ray (CXR) and liver function tests that revealed no abnormalities. Pulmonary function testing well demonstrated as there were no abnormalities.

**Assessment and Options for Treatment**
This patient is a 49-year-old man with T3N0M0 carcinoma of the glottic larynx involving the paraglottic space. Treatment options for this patient include the following:

1. **Total laryngectomy with ipsilateral neck dissection.** The likelihood of occult metastases in this patient is greater than 20%, necessitating a neck dissection despite the absence of clinically or radiologically positive nodes. Adjuvant radiotherapy will be dictated by pathologic staging. This patient may undergo voice rehabilitation with a tracheoesophageal prosthesis or electrolarynx. However, given the need for speech as part of his occupation, the patient may elect for other therapeutic options.

2. **Combined chemo- and radiotherapy.** The patient may elect to attempt for organ preservation measures because of his occupation. Based on the RTOG 91–11 study, radiotherapy alone would not be appropriate in this stage III lesion. Concurrent chemoradiation may allow for potential organ preservation. This patient is a candidate for nonsurgical management because there is no cartilaginous invasion through the thyroid cartilage, the arytenoid is mobile, there is no extralaryngeal spread, and there is an absence of subglottic extension.

3. **Function preservation surgery.** The patient may be a candidate for open transcervical function preservation therapy. Given the mobility of the arytenoid in addition to absence of thyroid cartilage invasion and any significant subglottic extension, the patient may be managed with supraccoid partial laryngectomy with cricohyoidepiglottopexy (SCPL-CHEP). Overall survival and local control would be comparable to other treatment options. However, voice outcomes...
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may be inferior to nonsurgical options, and consideration must be given to the patient’s pulmonary reserve status given the risk for postoperative aspiration.

Because of the patient's desire for function preservation, he was managed with primary chemoradiation and following completion of therapy underwent a complete response. Given the absence of neck disease posttreatment, neck dissection was not performed. Follow-up PET/CT every 3 months following therapy for the first year demonstrated no evidence of recurrent disease.

15.9.2 Case 2: T1N0M0 Glottic Cancer

Presentation

The patient is a 55-year-old man with a 25-pack-year smoking history who presents with a 9-month history of hoarseness. He denies any associated dysphagia, odynophagia, or otalgia.

Physical Examination

Examination is only remarkable for a left-sided plaque-like lesion along the true vocal cord. The cord is fully mobile, with no clear extension into the supraglottic larynx. Palpation of the neck reveals no clinically evident nodes.

Diagnosis and Workup

The patient undergoes direct laryngoscopy with biopsy. Examination under anesthesia reveals no anterior commissure involvement, with the tumor extending to the left vocal process. However, upon reoperative exposure, there is no extension grossly visible into the supraglottic larynx. Palpation of the N0 region under anesthesia reveals no anterior commissure involvement. The patient also had a CXR and obviates the need for surgical management of the N0 nodes.

Assessment and Options for Treatment

This patient is a 55-year-old with T1aN0M0 carcinoma of the larynx. Treatment options for this patient include the following:

1. Surgical management. This patient is a candidate for transoral surgical excision of the tumor. The tumor is early stage (T1a), with full visualization possible via a transoral approach. There is no extension into the anterior commissure which may otherwise preclude full visualization and is associated with a higher incidence of extralaryngeal extension and worse outcomes. The absence of subglottic and paraglottic involvement minimizes the risk of lymphatic spread and obviates the need for surgical management of the N0 neck. Surgery would be performed with transoral laser microsurgery (TLM). It should be noted that transoral excision may need to be repeated multiple times to achieve full local control, and also require frequent surveillance in the immediate postoperative period.

2. Radiotherapy. The patient may elect to undergo radiotherapy for management. Monotherapy would be appropriate in this early-stage lesion, with excellent local control and overall survival. However, use of radiotherapy may preclude further use in the setting of recurrence and should be discussed with the patient.

3. Function preservation surgery. The patient may be a candidate for open transcervical function preservation therapy. This is a localized early lesion to the true vocal cord without extralaryngeal spread. The patient may be a candidate for a vertical partial laryngectomy. However, given the localizing nature of the lesion and ability for full exposure through transoral approaches, a VPL would likely result in inferior functional outcomes compared to TLM.

The initial management decision was to perform transoral excision of the tumor. However, upon reoperative exposure, there was evidence of disease at the anterior commissure with resulting progression limiting full exposure. The decision was subsequently made to salvage with radiotherapy without treatment of the ipsilateral neck. The patient remains disease free at 3-year follow-up.

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16 Reconstruction of Laryngeal and Hypopharyngeal Defects

Han Zhang, David P. Goldstein, and John R. de Almeida

16.1 Introduction

Laryngeal and hypopharyngeal cancers together are the second most common cancer of the head and neck behind oropharyngeal cancer.1 Over 40% of laryngeal and hypopharyngeal cancers present with advanced-stage disease requiring complex multimodal treatment.2 Patients with early-stage disease may be treated with laryngeal preservation approaches while those with advanced disease may be offered laryngopharyngectomy.

Since the findings of the Veteran’s Affairs trial, many laryngeal cancers are treated primarily with chemoradiotherapy as a means to laryngeal preservation.3 As such, surgery is often reserved for salvage after local failures. Following radiotherapy and chemotheraphy, poor wound healing can lead to wound breakdown, infection, and pharyngocutaneous fistula in as many as 25 to 30% of patients.4,5 Exposure of great vessels after wound breakdown can further lead to catastrophic complications.4,5

The pharynx is encircled by the horizontal muscle fibers of the cricopharyngeus, and the stylopharyngeus muscles, all lead to propulsion of the food bolus into the cervical esophagus. The superior, middle, and inferior constrictors which help with propulsion of the food bolus into the cervical esophagus, the esophageal phase of swallowing is triggered and the pharyngeal phase of swallowing concludes.

The cervical esophagus is contiguous with the postcricoid region of the hypopharynx. It extends from the inferior border of the cricoid cartilage to the clavicles. The cervical esophagus helps to propel the food bolus from the hypopharynx down toward the superior and middle thoracic regions of the esophagus.

16.1.2 Physiologic Considerations

Swallowing is a complex function with four established phases: (1) oral preparatory phase, (2) oral phase, (3) pharyngeal phase, and (4) esophageal phase. Once food has been prepared in the oral preparatory and oral phases, the food bolus is propelled between the tongue and the palate, triggering the pharyngeal phases. The superior, middle, and inferior constrictor muscles of the pharynx are then responsible for the contraction and propulsion of the food bolus into the upper esophagus. Once the food bolus moves through the cricopharyngeus sphincter into the cervical esophagus, the esophageal phase of swallowing is triggered and the pharyngeal phase of swallowing concludes.

The larynx functions prominently in airway protection and respiration made possible by the three valves aforementioned. Systematic closure of the glottis followed by the false vocal cords, then the epiglottis to the arytenoids is essential in separating swallowing and respiration. Elevation of the larynx and pharynx via the vertically oriented salpingopharyngeus, palatopharyngeus, and stylopharyngeus muscles, all lead to movement of the food bolus into the cervical esophagus with protection of the airway. This complex reflex is highly coordinated and is often functionally impaired in the postsurgical head and neck cancer (HNC) patient. Therefore, special attention and consideration are needed for functional airway and swallowing separation.

16.1.1 Anatomy

The upper aerodigestive tract (UADT) is a complex anatomical area. The larynx, found in the anterior neck at the level of C3 to C5 vertebrae, functions in airway protection, phonation, and respiration made possible by a valve system. There are three valves within the larynx that include the true and false vocal cords, and the epiglottis. Coordination and adequate function of the valves are essential in preventing aspiration, airway obstruction, and changes in voice.
Reconstruction of Laryngeal and Hypopharyngeal Defects

Organ-preservation protocols and conservation laryngeal surgeries have helped improve vocal outcomes for UADT cancer patients. However, patients with advanced or recurrent cancer in the laryngopharyngeal region often still require total laryngectomy in the course of their treatment. Vocal rehabilitation in the form of alaryngeal speech often consists of three methods: electrolarynx, esophageal speech, and tracheoesophageal speech (TE). Selection of the best option for the postsurgical patient is an important consideration that should be evaluated in conjunction with a speech–language pathologist (SLP) and the individual characteristics of the patients.

16.1.3 Defect Classification

Reconstructive strategies for defects of the UADT depend on the extent of the defect after oncologic ablation. The ultimate goal is to restore function to the region with respect to the three main functions of speaking, swallowing, and breathing. Different subsegments of the UADT plays a unique part in achieving each of these functions. Hence, a systematic approach needs to be embraced for adequate functional reconstruction of this complex area. This chapter will cover the following defects: partial pharyngectomy with intact larynx (Fig. 16.1a), total laryngectomy with partial pharyngectomy (Fig. 16.1b), and total laryngopharyngectomy with circumferential pharyngeal resection (Fig. 16.1c).

16.2 Reconstructive Options

16.2.1 Partial Pharyngectomy Defect

Partial pharyngectomy defects are often small defects that are amenable to different forms of local closure options. Defects of this region can be further classified into posterior or lateral pharyngeal wall. The ultimate goal of the repair in these regions is the restoration of movement of the pharyngeal wall and watertight closure in order to facilitate breathing and swallowing functions. Several options are available for defects of this description including primary closure, local or regional flaps, and free tissue transfer.

Note

The ultimate goal of partial pharyngectomy reconstruction is the restoration of movement of the pharyngeal wall and watertight closure in order to facilitate breathing and swallowing functions.

16.2.2 Posterior Pharyngeal Wall

Small defects of posterior pharyngeal wall without cervical communication often can be left to heal secondarily or closed with split-thickness skin grafts. In instances where the posterior pharyngeal wall defect can be primarily reapproximated with sufficient tissue laxity to prevent stenosis formation, a primary closure can be attempted. This must not be attempted in defects larger than 2 to 3 cm in size or in patients with compromised wound healing such as radiated tissues.

Note

The lack of sensation associated with posterior pharyngeal reconstruction, in particular, those that extend to the esophageal inlet, impact swallowing in a way that may result in persistent aspiration.

16.2.3 Lateral Pharyngeal Defects

Small defects in the lateral aspect of the piriform sinus, similarly, can be closed either primarily or left to heal secondarily particularly if there is no cervical communication. Postoperative complications including fistulae, infection, and stenosis are often rare in the well-selected nonirradiated patient. Ideally, closure should be free of unnecessary tension in order to prevent postoperative pharyngeal stenosis.

Oftentimes certain factors such as type of ablation, prior radiotherapy, depth of the resection as well as whether neck dissection was performed can guide the form of reconstruction. A variety of local and regional rotation flap options exist to help bolster reconstructions of the hypopharynx. Local muscle flap options such as the digastric, stylohyoid, or sternocleidomastoid muscle flaps may serve to reinforce primary closure suture lines of the lateral or posterior pharyngeal wall often in the setting of prior radiotherapy. These muscle flaps may also be rotated into small defects with the mucosal aspect allowed to remucosalize. The caveat to muscle flaps is that they tend to contract and narrow the caliber of the hypopharyngeal lumen. On the other hand, these flaps tend to remucosalize with senescent mucosa which is particularly helpful in minimizing subsequent aspiration.

If the defect is larger than 3 cm in size, consideration has to be given regarding any severe distortion to the anatomy leading to swallowing impairment. In these cases, regional, or free tissue transfer may serve as better reconstructive options. Regional flap options that provide a cutaneous component to minimize the risk of stricture include the submental island flap (Fig. 16.2a, b), the supraclavicular island flap, the deltopectoral flap, or the pectoralis myocutaneous flap. Regional flaps are good options in patients with significant comorbidities and in whom operative time must be minimized as well as in centers without microvascular expertise. Free tissue transfer may also serve to reconstruct hypopharyngeal defects. Flaps such as the radial forearm flap may be used to reconstruct partial pharyngeal defects.
Fig. 16.1 Laryngectomy defect classifications: (a) partial pharyngectomy defect with intact larynx; (b) total laryngectomy defect; (c) total laryngectomy with circumferential pharyngeal defect.
For both posterior and lateral pharyngeal wall defects, care must be taken to avoid bulky flaps that place the patient at subsequent risk of aspiration, particularly in patients who are not undergoing total laryngectomy. If insensate tissue is being placed to reconstruct the hypopharynx, one must counsel patients about the risk of aspiration and efforts must be taken to minimize the amount of insensate tissue in the region of laryngeal introitus.

**Note**

The advantages of muscle flaps are that they provide reliable healing and will remucosalize. The disadvantage is that they may contract and narrow the caliber of the hypopharyngeal lumen.

Tumors involving the medial aspect of the piriform sinus or those involving the postcricoid region often require partial or total laryngectomy in conjunction with the partial pharyngectomy and will be covered in a subsequent section.

### 16.3 Total Laryngectomy, Partial Pharyngectomy Defect Management Options

Total laryngectomy defects with a partial defect of the pharyngoesophageal segment are often amenable to different forms of regional closure options. Depending on the amount of usable pharyngeal tissue that is present after ablation, several options including primary closure, pedicled local tissue transfer, and free tissue transfer are available. The ultimate goal within this region is a watertight seal in order to facilitate respiratory and swallowing functions. A secondary goal is the utilization of different techniques to restore speech function which will be discussed later within the chapter.

#### 16.3.1 Primary Closure

The presence of usable native mucosa that extends the entire length of the distance from the hypopharynx to the cervical esophagus helps to facilitate primary closure (Fig. 16.3a, b).
Adequate closure with avoidance of stenosis is a key principle to this form of closure. The lack of a circumferential scar helps prevent distal and proximal stenosis which in turn improves swallowing outcomes. Postoperative comorbidities including fistulas, infection, and stenosis are infrequent in the well-selected nonirradiated patient. Ideally, closure should be free of unnecessary tension in order to prevent postoperative stenosis of the area (Fig. 16.4b). Minimum amounts of residual pharynx required to prevent any severe distortion to the anatomy leading to swallowing impairment has been previously shown to be widths of 1.5 to 2.5 cm.10 In cases where less than 1.5 cm of usable mucosa remains, more advanced reconstructive options should be considered.

Primary closure methods and suture techniques vary depending on preferences of the surgeon. For the most part, it has been our experience that different closure patterns and suture techniques do not affect the likelihood of fistula development (Fig. 16.4a). Several studies have compared T-type closures with linear vertical closures, and there is little evidence to suggest any difference between these two methods with regard to fistula formation (Fig. 16.4b).11,12 However, in two small studies, patients that were primarily closed with a continuous Connell type suture (Fig. 16.4c) had a lower likelihood of fistula formation compared with interrupted suture technique (Fig. 16.4d) perhaps suggesting that continuous closure may be superior. There have been some limited studies with mixed results evaluating mechanical stapling devices for pharyngeal closure. One study suggested primary closure using mechanical stapling to be superior to suturing techniques in preventing fistula formation (7 vs. 37%, p = 0.0047).13 However,
several other studies suggest comparable rates to traditional suture techniques.14,15

**Note**
Reconstruction of the pharynx requires at least 1.5 cm of healthy mucosa. When there is less than 1.5 cm of mucosa, advanced reconstructive options should be considered.

### 16.3.2 Primary Closure with Bolster Flap

Results from the Department of Veteran’s Affairs Laryngeal Cancer Study Group study in the 1990s and the Radiation Therapy Oncology Group 91–11 (RTOG 91–11) study in 2003 ushered in a new era of organ-preservation treatment regimens utilizing chemotherapy and/or radiotherapy.3,16 As a result, salvage total laryngectomy with varying degrees of pharyngeal defects increased in numbers. However, because of the local tissue changes from chemoradiotherapy, rates of pharyngocutaneous fistulas have been an ongoing problem, reported in the literature to be at least 30%.17 In addition to this, major wound complication rates are noted to be upward of 50 to 60%.18 Certainly many preoperative predictors have been established within the literature, which can include low postoperative hemoglobin level, preoperative radiotherapy and/or chemotherapy, hypothyroidism, and concurrent neck dissection.4

Because of the propensity of major wound complications from salvage laryngectomy patients, reconstruction with various flaps have been investigated and shown to decrease fistula rates along with faster healing rates.18,19,20 Utilization of local pedicled myocutaneous flaps as well as free tissue transfer has both been advocated for utilization in salvage setting either as patches or as onlay grafts for better support. Options for local pedicled myocutaneous flaps include pectoralis major, deltopectoral, and supraclavicular flaps all have been advocated and shown within the literature to decrease fistula rates and wound complications.5,6,19

Among the breadth of free flaps available for reconstruction, a few unique options have arisen within the literature within the past decade. Utilization of the serratus anterior free flap based on the serratus branch of the thoracodorsal artery and the temporoparietal free flap have been advocated as a patch repair for salvage laryngectomy patients.21,22

The serratus anterior free flap has been described for reconstruction of various head and neck defects since its introduction in 1982. The muscle inserts anteriorly on the first nine ribs and derives its blood supply from perforators of the lateral thoracic artery, angular artery, and the thoracodorsal trunk. Because of the various branching patterns and perforator supply to the serratus, there is a lot of versatility that exists in terms of the size and bulk of the muscle that can be harvested. Khan et al described seven cases with patients who received salvage laryngectomy reconstructed with serratus anterior free flap onlay after primary closure of the pharynx (Fig. 16.5a, b).21

Temporoparietal fascia free flap has become a useful tool in the reconstruction of a variety of defects. Because of its ultra-thin, highly vascular, and low donor-site morbidity, it has become increasingly popular choice for head and neck reconstructions. Based on the superficial temporal artery and vein, it may be transferred independently or in combination with skin and potentially even calvarial bone. Higgins et al reported a unique usage of the temporoparietal fascial graft as a pharyngeal closure reinforcement for the reduction of pharyngocutaneous fistula in salvage laryngectomy patients.22 Among 12 patients, only one patient had a pharyngocutaneous fistula that responded with wound packing. Two patients had minor complications that were also treated with conservative therapy. All patients were tolerating a normal diet 3 months after the operation.

**Note**
The rate of wound complications following salvage laryngectomy are unacceptably high. The use of well-vascularized tissue to bolster or augment pharyngoesophageal reconstruction has proven helpful in decreasing complications.

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**Fig. 16.5 Total laryngectomy defect with primary closure and serratus free flap in-lay.** (a) serratus free-flap design; (b) primary closure with serratus free-flap in-lay.
16.3.3 Patch Reconstruction: Regional Tissue Transfer

Utilization of regional tissue transfer is a useful option for certain pharyngoesophageal defects in modern clinical practice. As previously discussed, regional flaps can often be used for small lateral pharyngeal wall defects in primary surgery patients or as an onlay flap for fistula prevention in the salvage laryngectomy patient. In the case of larger defects, regional flaps are rarely used and often reserved for patients who are at a high risk to undergo more complex methods of reconstruction because of severe medical comorbidities. Local tissue such as the pectoralis major myocutaneous, deltopectoral myocutaneous, and latissimus dorsi myocutaneous flaps are all viable options. While great alternatives to free flaps, these regional tissue transfers do have limitations. Bulkiness of the myocutaneous paddles, pedicle length limitations, reduced pliability, and a propensity to have partial flap necrosis particularly of the distal aspect of flaps are some of the disadvantages. However, in the vessel-depleted neck and in specific situations, these flaps can serve as a great tool in the reconstructive surgeon’s arsenal.

Pectoralis Major Myocutaneous Flap

The pectoralis major myocutaneous flap has been utilized for reconstruction of head and neck defects since the 1970s. The major advantages it offers over other regional flaps are its rich vascularity, ability to incorporate a large cutaneous skin paddle, one-stage reconstructive ability, improved arc of rotation, increased bulk, primary donor-site closure, and the ability to cover inner and outer epithelial components. The pectoralis major flap can be designed with a skin island for lateral pharyngeal wall defects or with a myocutaneous component as an onlay graft for support in the salvage laryngectomy patient.

This flap has been shown to help reduce the risk of fistula formation particularly in patients who are undergoing salvage laryngectomy. A recent systematic review demonstrated a 22% reduction in pharyngocutaneous fistulas in patients reconstructed with pectoralis myogenous flaps compared to primary closure. Another multi-institutional study comparing three groups, those with primary closure, those with pectoralis onlay flaps, and those with interposed free tissue, demonstrated that pectoralis flaps were associated with the lowest fistula rate of 15% compared to 34% in primary closures and 25% with interposed free tissue. The addition of the muscle component of this flap is arguably the most important component of the reconstruction. It is generally felt that the muscle obliterates any dead space surrounding suture lines of pharyngeal closure and provides a vascularized buttress that prevents salivary leakage into the cervical dead space.

Potential Complications

- Pectoralis myogenous and myocutaneous flaps often have little difficulty reaching laryngopharyngeal defects.
- For defects requiring a cutaneous skin paddle, myocutaneous skin paddles should be designed based on an arc of rotation about the midpoint of the clavicle.

Reconstruction of Laryngeal and Hypopharyngeal Defects

- Cutaneous skin paddles should be adequate in diameter to reconstruct the mucosal defect if necessary.
- Circumferential laryngopharyngeal defects are not well suited for reconstruction with a pectoralis flap because of the bulk of the flap.
- Myocutaneous flaps in general may alter the nipple position and may have cosmetic implications particularly in women which must be considered prior to using this option.
- For females, an inframammary incision may disguise incision lines.
- Free tissue transfer or use of an alternative regional tissue flap option such as the suprachlavicular flap may avoid the unsightly asymmetric nipple positioning in patients.
- Myogenous flaps must cover the suture lines of a laryngectomy defect and often may be secured to prevertebral fascia adjacent to the neoesophagus and to the tongue base superiorly.
- Laryngectomy defects with cutaneous skin resections may be reconstructed with pectoralis myocutaneous flaps for internal lining, and skin grafting the myogenous portion on the cutaneous aspect of the defect.

Because of the consistent anatomy and dependability of pectoralis major flap, low incidences of complete flap failure have been reported in large case series. Total flap necrosis has been found to range between 1 and 7% on several studies. Partial flap necrosis is a more common problem occurring in up to 14% of patients. Skin paddle size and placement, pedicle compression, age greater than 70 years, obesity, and low nutritional status are some of the factors cited as contributing to flap necrosis. Harvesting of the pectoralis major flap has also yielded pulmonary complications including pneumothorax, pleural effusion as well as pleural atelectasis.

Despite being a versatile option for head and neck defects, utilization of the pectoralis major flap for defects that extend more cephalad on the face or scalp often puts increased strain and tension on the pedicle contributing to flap failures. In addition, pectoralis major flap reconstruction is often a poor option for circumferential defects of the laryngopharynx. In these situations, free flap reconstruction often serves as the more prudent option.

Note

While the pectoralis myocutaneous flap provides a source of skin and vascularized muscle, this flap has several important limitations and therefore is not a first-line option for reconstruction in modern times.

Deltopectoral Fasciocutaneous Flap

Bakamjian popularized the use of the deltopectoral flap for head and neck pharyngeal reconstruction in the 1960s. Variability in flap design to reconstruct many different defects and with greater pedicle length are some of the advantages of this versatile flap.
Reconstruction of Laryngeal and Hypopharyngeal Defects

The deltopectoral flap can be designed a multitude of ways. It can either be used as a single-stage or two-stage reconstruction of laryngopharyngectomy defects. Bakamjian originally described the use of a two-stage deltopectoral flap for a controlled pharyngostoma which is then closed at a later date using a two-layered closure technique. As a single-staged procedure, it can be used for defects after a partial laryngectomy or a total laryngopharyngectomy. Often an island flap can be harvested closer to the deltopectoral groove with a subcutaneous broad-based pedicle incorporating the perforators for blood supply. Although of historical importance, utilization of the deltopectoral flap for patch reconstruction of total laryngectomy, partial pharyngectomy defects is no longer commonly used in modern laryngectomy reconstruction.

Potential Complications

- The deltopectoral flap may be a good regional flap option for skin resurfacing of the anterior neck particularly when there is tension on skin closures or skin has been resected with the tumor resection.
- Design of the deltopectoral flap should be based superior to incisions' need for pectoralis flap harvest in order to preserve the pectoralis flap for salvage situations.

Flap tip necrosis remains to be the most significant flap-related complication. This is often dependent on the length of the flap and the utilization of a delay procedure. Previously irradiated patients, infection, diabetes, along with nutritional compromise are other patient factors that may contribute to flap failure.

Previous case series has shown a failure rate of 9 to 16%.

Latissimus Dorsi Myocutaneous Flap

Despite being in the medical literature since 1896, utilization of the latissimus dorsi myocutaneous flap was first described for head and neck reconstruction in 1978 by Quillen et al. Advantages of the latissimus dorsi flap include an enlarged cutaneous pedicle, availability of thin and pliable muscle, increased arc of rotation, and the availability to fold the flap on itself. The flap can also be harvested as a pedicled or free tissue flap depending on the specifics of the defect requirements.

Design of the latissimus dorsi myocutaneous flap can be done as a muscular flap for support and inlay of total laryngectomy patients with primary closure as previously discussed or with a cutaneous paddle closure of the laryngopharyngectomy defect. As with deltopectoral flaps, rotational latissimus dorsi myocutaneous flap for total laryngectomy, partial pharyngectomy defects is largely historical and not a frequently used flap.

Potential Complications

Marginal flap necrosis is one of the potential complications of the latissimus dorsi flap. Pedicle twisting, improper design, and pushing the boundaries of flap size are common causes of flap necrosis. Care during passage of the flap through the tunnel into the neck along with judicious selection of flap size is necessary to prevent complications.

Brachial plexus injury is another major concern with latissimus dorsi flap harvest. Positioning of the flap during flap harvest has been implicated in causing this potentially devastating injury. Care in gentle retraction of the arm to prevent pressure is imperative in preventing this injury. Shoulder dysfunction from latissimus dorsi flap harvest is not uncommon. Studies have shown that despite initial impaired shoulder function in patients, range of motion often improved with time and physiotherapy.

Fasciocutaneous Free Tissue Transfer

The advent of microvascular techniques and free tissue transfer has significantly innovated reconstructive options for total laryngectomy defects. As a result, fasciocutaneous free flaps have become one of the most utilized reconstructive options for total laryngectomy with pharyngeal defects. Utilization of radial forearm and anterolateral thigh free flaps can be used for partial pharyngectomy defects as a patch or as previously discussed as a bolster in the salvage setting. The robust nature and versatility of fasciocutaneous free tissue allows it to be used in primary surgical as well as salvage cases. The major advantage is the availability of donor-site tissue, lack of morbidities, as well as the options of speech rehabilitation.

Radial Forearm Free Flap

Specific benefits of the radial forearm free flap for total laryngectomy with partial pharyngectomy defects is its thin and pliable tissue that is easily contoured compared to the thicker anterolateral thigh donor site. It also offers a rich blood supply to promote primary healing in salvage settings. Utilization of the antebrachial cutaneous nerve also allows for potential sensory restoration. The thin radial forearm can also be tubed and used for circumferential pharyngeal defects, which is discussed in a later section of the chapter.

Anterolateral Thigh

The anterolateral thigh donor site, much like the radial forearm, has the capability of providing a well-vascularized, thin, and pliable tissue that is ideal for the repair of partial pharyngectomy defects. However, studies have shown that anterolateral thigh flaps vary substantially in thickness depending on body habitus and as such, thickness of the tissue often becomes an issue in obese patients. The opportunity to harvest larger flaps and reduced donor-site morbidity are some of the potential benefits over the radial forearm free flap for total laryngectomy, partial pharyngectomy defects. Tubed anterolateral thigh free flap for circumferential pharyngeal reconstruction can also be accomplished and is discussed in a later section of the chapter.

16.4 Total Laryngopharyngectomy Defect Management Options

In comparison to partial pharyngectomy defects, total laryngopharyngectomy defects are associated with a higher postoperative complication rate and higher risk of long-term morbidity.

Note

Pedicle regional flaps such as the latissimus flap and the pectoralis flap are limited as a means of pharyngoesophageal reconstruction because of tissue bulk and arc of rotation.
such as stricture compared to partial pharyngectomy. In the contemporary setting, circumferential pharyngeal defects usually necessitate free flap reconstruction options, although other options are possible. Choice of donor sites often depends on the surgeon’s experience, availability of tissue and tissue compliance, as well as the reported complication, donor site morbidity, patient habitus, and prior treatments. Tensionless proximal and distal closures are important in preventing stenosis and fistula formation.

16.4.1 Enteric Flap Transposition

Enteric transposition flaps may be utilized for total laryngectomy defects with a circumferential pharyngeal defect. Utilization of either gastric pull-up or colonic interposition is especially useful in patients with extended cervical and thoracic esophageal involvement. In these cases, a distal anastomosis is difficult or impossible with a tubed free tissue reconstruction. In cases where the esophageal defect extends intrathoracic, sometimes a distal anastomosis can be facilitated by manubriectomy, but often an enteric transposition may be used. These reconstructions allow for a single anastomotic site, potentially reducing fistula rates. The major disadvantage of these techniques is the need to open multiple body cavities and the consequent morbidity and mortality associated with these procedures. Patients with significant cardiopulmonary diseases, portal hypertension, gastric varices, and a history of gastric surgery are often poor candidates. However, this form of reconstruction provides a useful option in the carefully selected patient with the ideal defect.

16.4.2 Gastric Pull-Up

Since its initial introduction by Ong and Lee in 1960, gastric transposition is an especially useful technique for circumferential pharyngectomy defects that extend into the thoracic esophagus. Gastric transpositions often result in one cervical anastomosis and is based on the right gastric and gastroepiploic vessels. The left gastric and short gastric vessels are often ligated to help facilitate the movement of the esophagus.

Potential Complications

The major disadvantage of the procedure is the mobilization of the esophagus through the thoracic and abdominal cavity. Our institution previously demonstrated that gastric transposition is associated with increased risk of wound-related complications, fistula, and total complications. In this study, gastric transpositions was associated with a complication rate of 86%, a fistula rate of 48%, and a stricture rate of 29%. Still other series report other potentially fatal complications such as carotid artery blowout of 6% and other significant complications such as delayed gastric emptying. In hospital mortality, one series was reported as 5%, In addition, patients with previous history of cardiopulmonary disease, portal hypertension as well as previous gastric surgery are poor candidates for this procedure. The most common problems encountered as a result of the procedure include pneumonia, persistent pleural effusion, and pneumothorax. The utilization of this procedure in the salvage setting is also associated with potentially high anastomotic leaks and is a potential contraindication.

16.4.3 Colonic Interposition

Colonic interposition is another form of enteric interposition transfer that has been described for the reconstruction of laryngopharyngeal defects. While initially popular in the 1960s, it has largely fallen out of favor due to its numerous disadvantages as compared to gastric transposition. High risk of anastomotic leaks up to 50% and abdominal complications along with patient mortality up to 20% are some of the issues facing colonic interposition grafts. However, this form of reconstruction may continue to have a very limited utility in certain situations. Given that the transposed colon can be tunneled into the pharynx, in selected cases where the esophagus is unavailable either due to caustic ingestion or advanced extraluminal esophageal cancer, this technique can be utilized.

Potential Complications

Mortality rate for colonic transplantation has been reported to be as high as 20%. Reconstructive complications including organ necrosis, fistula formation, and stenosis are up to 25%. Abdominal, thoracic, and medical complications are present in up to 45% of patients. Because of the colon’s propensity to becoming distended and atonic after transposition, a considerable amount of dysphagia is presented after reconstruction.

16.4.4 Microvascular Enteric Flaps

Jejunal and gastro-omental free flaps are both forms of microvascular enteric flaps. Both these free flaps allow for a secretary gastrointestinal mucosa with readymade mucus production which helps to facilitate swallowing functions. Relatively low perioperative morbidity associated with the ability to perform an immediate single-stage reconstruction coupled with an abundant source of donor site makes it a viable option for patients with circumferential pharyngeal defects.

Jejunal Free Flap

Seidenberg et al first reported use of a free jejunal flaps in pharyngoesophageal reconstruction back in 1960. This form of reconstruction is associated with a high risk of wound-related complications, fistula, and mortality. This donor site should be used with caution.
Reconstruction of Laryngeal and Hypopharyngeal Defects

reconstruction for the laryngopharyngectomy defect gained popularity in the 1980s mainly due to low perioperative mortality, the availability of a readymade mucosal tube, and the ability to perform an immediate single-stage reconstruction. The major drawback of this technique is the limitation of alar cartilage for reconstruction. Many describe the speech quality as a “wet” quality. Furthermore, swallowing may be impaired by uncoordinated peristalsis causing intermittent dysphagia.

The jejunum can be used as a mucosal tube or as a tube depending on the configuration of the defect. Preoperative assessment needs to exclude the absence of recipient vessels and the extension of disease into the thoracic esophagus. Patients need to also be examined to determine the absence of ascites and other chronic intestinal diseases such as Crohn’s disease or previous extensive abdominal surgeries. Utilization of antimicrobial prophylaxis preoperatively and postoperatively is essential in jejunal flap harvest. The size of the flap is determined by the dimensions of the defect. The segment of flap must be supplied by a single vascular arcade and is usually harvested within 150 cm distal to the ligament of Treitz.

Because of the poor tolerance of jejunum for prolonged ischemia time, the flap should be maintained by its vascular arcade pedicle until the recipient site has been prepared. Other considerations and precautions should also be taken to help increase the tolerance of jejunum to ischemia time. Limitation of ischemia time should be less than 2 hours to prevent reperfusion issues. Increased ischemic tolerance can also be increased by instituting hypothermia during the flap harvest and until reperfusion has been accomplished.

**Potential Complications**

Successful transfer often occurs within 91% of cases with a fistula rate of 18%. A range of abdominal complications can be instigated from the flap harvest. Wound dehiscence, bowel obstruction, gastrointestinal hemorrhage, G-tube leakage, and prolonged ileus have been reported to occur up to 5.8%.

**16.4.5 Microvascular Fasciocutaneous Flaps**

Utilization of radial forearm and anterolateral thigh free flaps can be used for partial pharyngectomy defects as a patch or when previously discussed or circumferential defects as a tubed reconstruction. Tubed fasciocutaneous flaps provide good swelling outcomes and relatively low morbidity by avoiding entry to multiple body cavities.

**Radial Forearm Free Flap**

First introduced by Yang et al in 1981, the radial forearm free flap has become a staple in intraoral reconstruction. This versatile and reliable flap may be transferred as a fasciocutaneous, composite, and or innervated free tissue. The major advantages of the radial forearm lie within its thin pliable skin, rich vascularity, which allows for a high degree of reliability and flexibility in design.

The skin of the entire forearm, extending from the antebrachial fossa to the flexor crease of the wrist can be harvested. The thickness of the flap tends to vary among patients but is thinner toward the wrist crease. Multiple designs and templates have been contemplated for the radial forearm free flap for all forms of head and neck defects. For total laryngopharyngectomy defects, the forearm tissue may be tubed for circumferential reconstructions depending on the pharyngeal defect left after oncologic ablation.

**Potential Complications**

Anatomy of the palmar arch is fairly consistent with a complete superficial palmar arch reported in 77.3% of cases. Testing with Allen’s examination along with oxygen saturating testing is essential in preventing catastrophic complications. Poor skin graft uptake at the donor site may also result, typically from shearing forces of the underlying muscles due to inadequate mobilization. Sensory loss following injury to the superficial branches of the radial nerve and transection of the antebrachial cutaneous nerves is also common.

**Note**

Reconstruction of a circumferential pharyngoesophageal defect with a radial forearm free flap may require a large skin paddle. This may be associated with significant donor-site morbidity including sloughing of the skin graft and decreased range of motion in the donor arm.

**Anterolateral Thigh Free Flap**

Baek introduced the possibility of basing a thigh flap on a direct cutaneous perforator in 1983. Hayden further popularized the lateral thigh flap and demonstrated its utility in head and neck reconstruction in 1994. Since that time, usage of the lateral thigh for head and neck defects has been innovated for various subsites including the total laryngectomy with pharyngectomy defects. Most commonly, the anterolateral thigh free flap is used as a tubed reconstruction for circumferential pharyngeal defects (► Fig. 16.6).

Design of the cutaneous paddle should be done in an area two-thirds to three-quarters anterior to the surface of the septum. Maximum dimensions of the skin paddle that can be viable harvest has never been predetermined. Sizes have varied but have been reported to be up to 25 × 14 cm. Because of the increased thickness and rich vascularity, anterolateral thigh is the preferred donor site as a tubed reconstruction for circumferential pharyngeal defects at the author’s institution.

**Potential Complications**

Predominance of the cutaneous perforators within the lateral thigh can be highly variable. Up to 15% of the population may have a dominant second or fourth perforator. Dissection in
these cases might involve a more distal or proximal skin paddle. Lower extremity ischemic or atherosclerotic injuries are other potential complications that can compromise the flap viability. Although no lower extremity angiographic studies are required for anterolateral thigh flap elevation, care needs to be taken when patients present with lower arterial disease histories.

Potential donor-site morbidity from ambulation can potentially be problematic particularly among the elderly population. Depending on the size of the skin paddle harvested from the thigh, primary closure of the donor site can sometimes yield compartment syndrome. Although this complication is rare, care and attention to the tension along the donor site closure need to be taken.

16.5 Salivary Bypass Tubes

Many centers advocate the use of salivary bypass tubes particularly for tubed flap reconstruction of a neoesophagus. Salivary bypass tubes provide a diversion conduit for saliva and purport to minimize exposure of suture lines to salivary contamination. Although in the absence of large-scale studies, it is difficult to establish any benefit, there are reports of a reduction in fistula rates using bypass tubes.60 Any potential reduction in long-term stricture is less clear-cut. At our institution, salivary bypass tubes are removed 3 to 4 weeks after surgery when used. Cicatricial scar formation at anastomotic sites are likely to continue to form well after removal of bypass tubes.

16.6 Swallowing Rehabilitation

Restoration of normal deglutition is a key aspect to improving quality of life among laryngectomy patients.61 Depending on certain patient and surgical factors, time to initiate swallow can often vary. Healthy patients without nutritional compromise and lack of previous radio- and/or chemotherapy can often be initiated with swallowing on the fifth to seventh day after surgery. Patients receiving salvage laryngectomy often require longer healing times with swallowing to be initiated on the seventh to tenth day after surgery. Swallowing therapy from a dedicated head and neck trained speech–language pathologist can also not be overestimated. Therapies in these cases are imperative to the restoration of a safe and adequate swallowing function with the ultimate goal of avoiding a long-term feeding tube insertion.

16.7 Voice Rehabilitation

The loss of the ability to verbally communicate after a total laryngectomy has psychosocial consequences and may be associated with impairment in quality of life. As a result, effective
voice restoration is essential for the rehabilitation of these patients. Currently, three methods of alaryngeal speech exist: electrolarynx speech, esophageal speech, and tracheoesophageal (TE) speech. Esophageal speech utilizing air that is injected into the cervical esophagus and expelled causing pharyngoesophageal mucosal vibration despite being an effective method of voice rehabilitation is difficult to learn. In fact, only about 26% of patients are able to use this method on a daily basis.62 Tracheoesophageal puncture (TEP) as a result has become the gold standard for voice restoration. Since its first introduction by Singer and Blom in 1979, this method of surgical voice restoration is di

Singer and Blom in 1979, this method of surgical voice restoration is di

References

Note

Fasciocutaneous free flap reconstruction often produces more consistent voice rehabilitation with clearer vocalization quality when compared with an enteric flap reconstruction.

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16.8 Conclusion

Reconstruction of the laryngopharyngectomy defect can pose a significant challenge to the head and neck reconstructive surgeon. The desire to create a safe wound while considering the functional aspects of swallowing and voice rehabilitation can be extremely difficult. Principles of reconstruction in this physiologic complex area should center on the creation of a safe wound devoid of fistula formation, the restoration of normal deglutition, and the ability to achieve voice rehabilitation. Advancement in the past two decades has increased the options available to the head and neck reconstructive surgeon allowing for patient-tailored treatment regimes. As more innovations are brought forward in the future, appropriate patient selection combined with meticulous operative planning remains the foundations of success.

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17 Carcinoma of the Thyroid

17.1 Introduction

Thyroid carcinoma is a growing national health care concern. Nearly 300,000 new cases of thyroid cancer were diagnosed worldwide in 2012, making it the 16th most common cancer in the world.1 Approximately 63,000 new thyroid cancers were diagnosed in the United States alone in 2014.2 The yearly incidence of thyroid cancer in the United States has nearly tripled from 4.9 to 14.3 per 100,000 individuals between 1975 and 2009. This increased incidence has disproportionately affected women, who are three times more often to be diagnosed with thyroid cancer than men. This dramatic rise in incidence can be almost completely attributed to an increase in papillary thyroid carcinoma, particularly lesions less than 1 cm.3 Based on these current incidence trends, projected U.S. health care costs for thyroid carcinoma alone in the year 2030 will exceed $3.5 billion.4 Despite the increased incidence of thyroid carcinoma in the United States, mortality rates have remained stable over the same period of time. Interestingly, this suggests that the rise in thyroid cancer diagnoses is due to an epidemic of detection (the result of more imaging studies being performed and more careful pathologic scrutiny of surgical specimens) rather than a true increase in the incidence of thyroid carcinoma.3 The challenge facing the future treatment of thyroid carcinoma, particularly smaller papillary thyroid cancers, will be to distinguish which cancers can be followed clinically and which require surgery.

17.2 Thyroid Anatomy and Embryology

17.2.1 Thyroid Anatomy

The thyroid is a butterfly shaped gland consisting of two lateral lobes connected by a central isthmus, weighing 15 to 30 g in adults. Each lobe varies from 40 to 60 mm in height with the superior pole wrapping posteriorly around the thyroid lamina and inferior constrictor muscles, while the inferior pole extends inferiorly to the level of the fifth to sixth tracheal rings. The isthmus ranges from 10 to 15 mm in height and typically overlies the second to fourth tracheal rings.2 A pyramidal lobe of varying size can be found in up to 55% of patients extending superiorly from either lobe or the isthmus, more commonly from the left (▶ Fig. 17.1).

The gland itself lies just deep to the strap muscles and is enveloped by layers of the deep cervical fascia. Two layers are typically encountered during surgery. The deep layer is a true capsule and interdigitates throughout the glandular tissue forming septae. The thinner, more superficial layer of fascia is a false capsule, loosely adherent to the true capsule. The enveloping fascial layers condense posteriorly to form Berry’s ligament, attaching the gland to the cricoid cartilage and the first several tracheal rings. This attachment accounts for the rise and fall of the thyroid during deglutition. Typically, the recurrent laryngeal nerve runs superficial to Berry’s ligament, but may also run through its most posterolateral aspect.

The arterial blood supply originates from the superior thyroid artery, arising from the external carotid artery, and the inferior thyroid artery, arising from the thyrocervical trunk. Infrequently, the thyroid ima artery arising most commonly from the brachiocephalic trunk may contribute blood supply when one or both of the inferior thyroid arteries are absent. More rarely, it may be the sole blood supply. The thyroid is drained by three paired veins. The superior thyroid vein, which runs in a vascular bundle with the superior thyroid artery, and the middle thyroid vein that empties into the internal jugular vein. The inferior thyroid veins drain into the left and right brachiocephalic veins. Occasionally, both these vessels may converge to form a common thyroid ima vein that drains into the left brachiocephalic vein.

Lymphatic drainage from the thyroid is quite variable and extends in all directions. The first echelon is typically either superiorly to the prelaryngeal nodes (Delphian), or inferiorly to the pretracheal and paratracheal nodes (level VI), then into the superior mediastinal lymph nodes (level VII). Drainage, however, may also occur laterally to levels II to V.

17.2.2 Embryology

The medial portion of the gland derives from the endoderm of the first and second pharyngeal pouches, which fuse to create a diverticulum at the foramen cecum of the base of tongue. It then descends along an anterior midline path during weeks 4 to 7 of gestation to its final pretracheal destination. The extension of tissue between the foramen cecum and the migrating thyroid gland is referred to as the thyroglossal duct. This duct normally obliterates; however, its persistence can lead to the development of a thyroglossal duct cyst or ectopic thyroid tissue. Persistent thyroid tissue at the distal end of this tract gives rise to the pyramidal lobe. The lateral portion of the gland is formed by the fourth and fifth pharyngeal pouches and descends in a similar but more lateral fashion to fuse with the medial gland. Remnant thyroid tissue along this more lateral path of migration may form the tubercle of Zuckerkandl (▶ Fig. 17.2). Parafollicular C cells, which arise from ectodermal neural crest cells of the ultimobranchial bodies, descend and fuse with the upper, lateral portion of the gland. These cells give rise to medullary thyroid carcinoma, which occurs in the upper one-third of the lateral thyroid lobes.
Knowledge of the following anatomical landmarks, both their classic locations and variants, is critical to performing safe thyroid surgery.

**Superior Laryngeal Nerve**

The superior laryngeal nerve (SLN) originates from the nodose ganglion of the vagus nerve superiorly in the neck. The SLN descends along an oblique anteroinferior course, deep to the internal and external carotid arteries, then splits into internal and external branches roughly 2 cm from the superior pole of the thyroid. The internal branch enters the thyrohyoid membrane posteriorly to provide sensation to the supraglottis. The external branch continues along the original path of the main trunk, traveling with the superior thyroid vascular pedicle (superior thyroid artery and vein) until approximately 1 cm above the superior pole, where it dives deeply to innervate the cricothyroid muscle. Ligation of the superior pedicle should be performed as close as possible to the superior pole to minimize injury to the external branch. Occasionally, the external branch will remain in close proximity to the superior pedicle until or below the level of the superior pole. If this is encountered, the SLN must be carefully dissected free from the pedicle and/or gland before ligating the vessels.

A non-recurrent laryngeal nerve (NRLN) is a rare variant observed most commonly on the right side in up to 1.6% of patients. It is associated most commonly with an aberrant right subclavian artery that branches from the descending aorta after the left subclavian artery takes off. Subsequently, it travels a retroesophageal course to reach the right side. If encountered, the NRLN branches from the vagus nerve at approximately the level of the cricoid and travels in a direct horizontal path to the laryngeal entry point (Fig. 17.3). If a computed tomography (CT) or magnetic resonance imaging (MRI) of the neck was included in the preoperative workup, evaluating the location of the right subclavian artery may help predict the presence of a NRLN.

**Parathyroid Glands**

Preservation of the parathyroid glands and their blood supply is critical in maintaining normocalcemia postoperatively. The superior parathyroid glands are typically found within 1 to 2 cm of the intersection of the RLN and the inferior thyroid gland. Ligation of the superior pedicle performed during thyroidectomy should be performed as close as possible to the superior pole to minimize injury to the external branch. The recurrent laryngeal nerve has extralaryngeal branches in up to 30% of patients; it is critical to preserve these branches, especially the anterior branch that innervates the larynx.
artery (ITA), along the posterior mid- to upper thyroid lobe, posterior to a coronal plane created by the RLN. The inferior glands are frequently located inferior to the neurovascular intersection, along the posterior mid- to lower thyroid lobe, anterior to the coronal plane created by the RLN (▶ Fig. 17.4).

Dissection just deep to the superficial fascia of the thyroid gland (described previously) will aid in protection of the parathyroid glands as they are separated from the thyroid. Preservation of the blood supply, which is predominantly from the ITA for both the superior and inferior glands, is also essential to maintaining postoperative function. If the blood supply is compromised, the devascularized parathyroid gland should be morselized and implanted into a strap muscle or the sternocleidomastoid muscle (SCM).

**Tubercle of Zuckerkandl**

As described above, the tubercle of Zuckerkandl is a lateral protruberance of remnant thyroid tissue from the embryonic migration of the lateral thyroid gland. It is present in 7 to 55% of patients and very consistently overlies the RLN just before it enters the larynx (▶ Fig. 17.5). To adequately visualize the tubercle of Zuckerkandl, the thyroid lobe must be retracted medially after release of its superior pole.

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**Fig. 17.3** View of right central neck compartment showing non-recurrent laryngeal nerve (black arrow) emerging from behind the carotid artery (C).

**Fig. 17.4** View of the left central neck compartment demonstrating the embryological relationship between the recurrent laryngeal nerve (black arrow) and the inferior parathyroid gland (white arrow), which is always ventral to the coronal plane of the nerve.

**Fig. 17.5** (a) Large left tubercle of Zuckerkandl (T). (b) Reflection of the tubercle of Zuckerkandl ventrally reveals the recurrent laryngeal nerve (black arrow) immediately beneath the tubercle.
17.3 Diagnosis and Evaluation of Thyroid Cancer

17.3.1 History

Several important factors may increase a patient’s risk for thyroid cancer. Females are three times more likely than men to develop differentiated thyroid carcinoma (DTC), and twice as likely to develop anaplastic thyroid carcinoma. Age is also important, as the incidence of thyroid cancer peaks in the late 40s for females and late 60s for males. Patients living in iodine-deficient regions and areas of endemic goiter have increased incidence of follicular thyroid carcinoma (FTC). A history of low-dose external beam ionizing radiation exposure, particularly before 10 years of age, whole-body radiation in preparation of bone marrow transplant, and exposure to ionizing radiation from nuclear fallout (such as the Chernobyl or Fukushima nuclear reactor disasters or atomic bomb detonation) greatly increase the risk of developing thyroid cancer later in life.

Family history is also important. Up to 6% of papillary thyroid carcinomas are hereditary, 30% of medullary thyroid carcinomas are attributed to autosomal dominant germline mutations, and several syndromes such as Gardner’s syndrome and Cowden’s disease are associated with papillary thyroid carcinoma. Symptoms of pain, dysphagia, and dyspnea and signs such as voice change, stridor, or rapid growth of a neck mass should all increase suspicion for thyroid malignancy, especially in the background of a known thyroid nodule.

Note

A history of low-dose external beam ionizing radiation exposure, particularly before 10 years of age, whole-body radiation in preparation of bone marrow transplant, and exposure to ionizing radiation from nuclear fallout greatly increase the risk of developing thyroid cancer later in life.

17.3.2 Physical Examination

A complete head and neck examination should be performed with special attention paid to palpating the thyroid gland, as well as the central and lateral neck compartments. Hard, fixed, and/or painful lesions increase suspicion for malignancy. Functional examination of the vocal cords using indirect mirror laryngoscopy or flexible nasopharyngoscopy is recommended in every patient before thyroid surgery, but especially if there is a suspicion for malignancy. Tracheoscopy and esophagoscopy are alternative to CT as a means to avoid iodinated contrast as well as radiation exposure to children and pregnant women. Positron emission tomography (PET) is not recommended in the initial workup of a thyroid nodule. Moreover, differentiated thyroid carcinomas and medullary thyroid carcinomas are generally not PET avid. Increased focal uptake in the thyroid noted incidentally on PET, however, should be worked up with FNA, as this finding is associated with an increased risk of malignancy.

Note

Thyroid US is the preferred imaging modality for the initial evaluation of a thyroid nodule.

17.3.3 Laboratory Assessment

In the setting of a known thyroid nodule greater than 1 cm, the American Thyroid Association (ATA) guidelines recommend serum thyrotropin (thyroid-stimulating hormone [TSH], normal range 0.4–5.0 mU/mL) to be obtained. If TSH is subnormal (suggestive of hyperthyroidism), a radionuclide scan is recommended for further evaluation. If the TSH is normal or elevated (suggestive of hypothyroidism), no radionuclide scan is needed and fine-needle aspiration (FNA) of the nodule is indicated to assess for malignancy. Serum thyroglobulin (Tg) assessment is not indicated in a patient who has a thyroid gland, as it is insensitive and nonspecific for malignancy in this setting.

17.3.4 Imaging

Thyroid ultrasonography (US) is the preferred imaging modality for the initial evaluation of a thyroid nodule. US of the central and lateral neck compartments is also recommended on all patients with known or suspected thyroid malignancy. While no longer routinely performed during the evaluation of thyroid nodules, a radionuclide scan with 123I or technetium 99 m sestamibi can be used to assess the risk for malignancy of a thyroid nodule. Malignant thyroid cells dedifferentiate and undergo loss of functional activity; therefore, hypofunctioning ("cold") nodules are at increased risk for malignancy and should undergo FNA. FNA should not be performed for isofunctioning ("warm") and hyperfunctioning ("hot") nodules.

Computed tomography can be considered if there is concern for invasion into adjacent structures, such as the larynx, trachea, or esophagus, that would alter the surgical management. The use of iodinated contrast, however, may result in stunning of differentiated thyroid carcinomas and cause delay in the use of adjuvant radioactive iodine (RAI). This delay is justified if the contrasted imaging will improve the oncologic resection. MRI is an alternative to CT as a means to avoid iodinated contrast as well as radiation exposure to children and pregnant women. Positron emission tomography (PET) is not recommended in the initial workup of a thyroid nodule. Moreover, differentiated thyroid carcinomas and medullary thyroid carcinomas are generally not PET avid. Increased focal uptake in the thyroid noted incidentally on PET, however, should be worked up with FNA, as this finding is associated with an increased risk of malignancy.

17.3.5 Fine-Needle Aspiration

Current ATA guidelines for performing FNA on thyroid nodules are based on both size and US characteristics. Benign-appearing nodules that are purely cystic are not recommended for FNA regardless of size because of such low risk for malignancy (< 1%). Very low suspicion nodules, characterized by spongiform or partially cystic findings, could be considered for FNA if greater than 2 cm. Conversely, it is reasonable to observe these nodules with serial US, as the risk for malignancy is less than 3%. Low suspicion nodules that are solid and isoechoic or hypoechogenic, or partially cystic with eccentric solid areas have a 5 to 10% risk of malignancy, and are recommended for FNA if they are ≥ 1.5 cm. Intermediate and high suspicion nodules that are
solid and hypoechoic should undergo FNA if greater than 1 cm. These nodules have a risk of malignancy ranging from 10 to 90% depending on the presence of irregular margins, microcalcifications, a taller than wide appearance on transverse imaging, or extrathyroidal extension.²

FNA cytology results are reported according to the Bethesda system (Table 17.1), which attributes an estimated risk of malignancy to each diagnostic category to help guide surgical decision making.³ For nondiagnostic or unsatisfactory specimens, FNA should be repeated. A benign diagnosis carries a 1 to 4% risk for malignancy. Surgery is not generally recommended for these nodules, unless there are other reasons to remove them (e.g., symptoms, patient desire). A malignant FNA result is associated with a 97 to 99% risk of malignancy and surgery is recommended.

Note

For the indeterminate nodule, patient history, clinical risk factors, personal preferences, and imaging findings should all be considered when formulating treatment recommendations.

The diagnosis of suspicious for papillary carcinoma (SUSP) has a predicted 60 to 75% risk for malignancy. The ATA guidelines for SUSP include a weak recommendation to consider mutational testing (BRAF or multigene panel: BRAF, RAS, RET/PTC, PAX8/PPARγ) to help further stratify the risk for malignancy and counsel patients on surgery. The ATA also has a strong recommendation that these lesions may be managed surgically in a manner similar to that of lesions with malignant cytology.²³

### 17.4 Differentiated Thyroid Carcinomas

Differentiated thyroid carcinomas arise from the follicular cell of the thyroid gland. They retain some degree of normal follicular cell function and structure, allowing iodine uptake and organification, as well as an intact p53 pathway for programmed cell death. Overall, they are less aggressive and have a better prognosis than poorly differentiated thyroid carcinomas. DTCs comprise greater than 90% of all thyroid carcinomas and include papillary thyroid carcinoma (PTC), FTC, Hürthle cell carcinoma (HCC), and their respective variants.²

#### 17.4.1 Papillary Thyroid Carcinoma

**Epidemiology**

Papillary thyroid carcinoma is the most common thyroid carcinoma in both adult and pediatric patients, accounting for greater than 80% of all thyroid malignancies. As stated above, the incidence of PTC, particularly lesions less than 1 cm, has continued to rise disproportionately to all other thyroid carcinomas. This is attributed primarily to an increase in diagnosis, rather than an epidemic in disease.³ The average age at diagnosis is 35 years and there is a greater than 3:1 female to male ratio.

**Etiology**

Papillary thyroid carcinoma primarily arises spontaneously, with low-dose radiation exposure (especially when <10 years of age) and hereditary syndromes accounting for less than 5% of PTCs. Syndromes associated with PTC include familial medullary thyroid cancer (FMTC), familial adenomatous polyposis (FAP), Cowden’s disease, Gardner’s syndrome, Werner’s syndrome, and Carney’s complex.
**Presentation**

Most PTCs are diagnosed as an asymptomatic palpable thyroid mass on physical examination or discovered incidentally on imaging. FNA cytology is highly sensitive and specific for PTC. PTC has a propensity for lymphatic spread; up to 30% of adult patients and 90% of pediatric patients present with regional neck disease at the time of diagnosis. \(^\text{10}\)

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**Note**

Most papillary thyroid carcinomas are diagnosed as an asymptomatic palpable thyroid mass on physical examination or discovered incidentally on imaging.

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**Treatment**

The ATA guidelines recommend total thyroidectomy for any PTC that is greater than 4 cm (T3, see staging, below), exhibits gross extrathyroidal extension (ETE, T4) on imaging, or is clinically N1 or M1. For any PTC greater than 1 cm but less than 4 cm (T1b and T2), without ETE, and clinically N0, surgery can be either total thyroidectomy or lobectomy for low-risk patients (no contralateral nodules, absent factors in history, no concerning histological or imaging features). For any papillary thyroid microcarcinoma (PTMC) (< 1 cm [T1a] without ETE and clinically N0), thyroid lobectomy alone may be sufficient treatment, unless there are clear indications to remove the contralateral lobe (similar to low-risk patient factors described above). \(^\text{2}\)

Although the current ATA treatment guidelines recommend surgery for any diagnosis of PTC, recent research suggests that there may be a role for surveillance of low-risk patients with PMC. Ito et al have demonstrated that low-risk PMCs rarely progress in size or develop regional spread, and if progression is noted, surgical outcomes are not compromised by the surveillance period. \(^\text{11, 12}\) Considering the epic rise in incidentally diagnosed PMCs and the potential future health care burden associated with operating on all of these patients, observation of low-risk PMCs may become a reasonable treatment option for selected patients.

With regard to management of the central neck, ATA guidelines have strong recommendations for therapeutic central neck dissection (CND) of any clinically involved lymph nodes (cN1a) and against elective central neck dissection for any PTC less than 4 cm (T1 and T2) that is also clinically node negative (N0). There is more ambiguity with PTCs greater than 4 cm and/or with ETE (T3 and T4) with clinically uninvolved central nodes (cN0) or clinically involved lateral neck nodes (cN1b). For this group of patients, there is a weak recommendation to consider elective CND. While limited data have suggested improved disease-specific survival, lower local recurrence rates, and decreased postoperative Tg levels after prophylactic CND, other studies have shown no improvement in long-term patient outcomes and an increased risk for postoperative complications, namely hypoparathyroidism and RLN injury. \(^\text{2}\) Furthermore, although elective CND in these patients does detect a substantial number of pN1 patients, effectively upstaging patients older than 45 years (see staging, below) and influencing the decision for adjuvant RAI, most of these nodes are only microscopically positive and may not have the same recurrence risk as macroscopically positive nodes. \(^\text{13}\)

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**Note**

With regard to management of the central neck, ATA guidelines have strong recommendations for therapeutic central neck dissection of any clinically involved lymph nodes and against elective central neck dissection for any papillary thyroid carcinoma less than 4 cm that is also clinically node negative. The ATA guidelines for lateral neck dissection are more straightforward. Strong recommendations exist for therapeutic lateral neck dissection for any biopsy-proven metastatic cervical lymphadenopathy (pN1b), and against elective lateral neck dissection even in the presence of clinically involved central nodes (cN1a). \(^\text{2}\)

**Adjunctive Therapies**

Radioactive iodine is used in several ways in the postoperative management of PTC. Remnant ablation is intended to destroy any residual normal thyroid tissue (<1 cm) with the goal to increase the specificity of surveillance methods and possibly increase disease-free survival. ATA guidelines suggest considering remnant ablation with a 30 mCi dose for intermediate-risk patients with PTC greater than 4 cm (T3), microscopic ETE, any N, and advanced age (>45 years). Adjuvant therapy, which is used to treat suspected but unproven residual microscopic disease, has been shown to increase both disease-free and disease-specific survival. Doses up to 150 mCi are recommended for any PTC with macroscopic ETE (any T4). RAI can also be used in the management of known persistent disease. Doses up to 150 mCi for locoregional disease or 100 to 200 mCi for metastatic disease not amenable to surgical resection are recommended, with the goal of increasing disease-specific survival and/or decreasing morbidity. Treatments may be repeated every 6 to 12 months for persistent disease if there continues to be a clinical response and the disease remains RAI avid. \(^\text{3}\)

There is no role for adjuvant external beam radiation therapy (EBRT) to the primary site or central or lateral neck compartments regardless of T and N stage if complete surgical extirpation of disease is achieved. In cases of persistent local or regional disease not amenable to surgical resection, particularly if RAI avidity is lost, EBRT can be considered as adjuvant or palliative therapy. At this time, there is no role for systemic adjuvant therapy, besides the previously discussed indications for RAI.

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**Note**

There is no role for adjuvant EBRT to the primary site or central or lateral neck compartments regardless of T and N stage if complete surgical extirpation of disease is achieved.
Carcinoma of the Thyroid

Variants
Several variants of PTC exist, categorized both by size and histology. PTMC is a subcategory of PTC and includes any lesion less than 1 cm (T1a) without ETE and clinically N0. PMCs generally have a much better prognosis than PTC, dictating less aggressive surgical management. As discussed previously, the true clinical significance of PMCs may be such that initial management will be medical surveillance in the near future. In general, histological variants of PTC such as tall cell, columnar cell, diffuse sclerosing, and insular are all more aggressive than classic PTC and should be managed accordingly. This is especially true for tall cell variants, which tend to be non-RAI avid. The follicular variant of PTC possesses a similar prognosis as classic PTC and should be treated in a similar manner.

17.4.2 Follicular Thyroid Carcinoma
Epidemiology
Follicular thyroid carcinoma is the second most common thyroid carcinoma, accounting for roughly 10% of all thyroid malignancies. While there has been a dramatic rise in the incidence of PTC in the United States over the past several decades due to increased diagnosis, the incidence of FTC has remained relatively stable at 1/100,000. FTC occurs more frequently in iodine-deficient regions and areas of endemic goiter, which explains its decreasing worldwide incidence secondary to iodine-supplementation initiatives. The average age at diagnosis is approximately 50 years, with a 3:1 female to male ratio.

Etiology
The majority of FTC is sporadic, however, there is an association with low-dose radiation exposure in childhood, albeit to a lesser extent than PTC. Syndromes such as FNMT, Cowden’s disease, Werner’s syndrome, and Carney’s complex contribute a small percentage to the overall incidence as well.

Presentation
Similar to other differentiated thyroid carcinomas, FTC typically presents as an asymptomatic palpable thyroid mass or is discovered incidentally on imaging. FTC has a propensity to spread hematogenously and therefore presents with relatively less regional disease (<10%) than PTC. Secondary to this hematogenous spread, however, distant metastases to the bone, liver, lung, and brain are more than twice as likely with FTC than PTC. As discussed earlier, FTC cannot be diagnosed on FNA cytology, and surgical excision is required for histological confirmation.

Note
Follicular thyroid carcinoma has a propensity to spread hematogenously and therefore presents with relatively less regional disease (<10%) than papillary thyroid carcinoma.

Treatment
The treatment for FTC typically begins with a lobectomy based on indeterminate FNA results (FLUS/AUS, follicular neoplasm [FN], or SFN). The decision for completion thyroidectomy is then based on the results of final pathology. Current ATA guidelines for DTC do not differentiate between PTC and FTC; however, several studies have shown that lobectomy alone is sufficient for minimally invasive lesions (<1 cm, no ETE, and cN0) with capsular invasion only and possibly for lesions with minimal vascular invasion (<three vessels). Completion thyroidectomy is generally recommended for all other T-stage FTCs, those with gross vascular invasion (≥three vessels), or high-risk features or history. ATA guidelines do not comment on the utility of frozen section analysis for FTC. While in theory this may save the costs of a potential second procedure, the reality is that frozen section analysis for FTC is not very reliable, with sensitivities ranging from 36 to 77% and specificities from 68 to 100%

Given that FTC is far less lymphotropic than PTC, the management of regional nodes is accordingly different. Both central and lateral neck dissections should only be performed for clinically evident disease in their respective compartments. There is no role for elective neck dissection.

Adjunctive Therapies
ATA guidelines for adjuvant therapies are the same for FTC as for PTC.

17.4.3 Hürthle Cell Carcinoma
Epidemiology
Hürthle cell carcinoma is a rare form of thyroid malignancy accounting for approximately 3% of all thyroid malignancies. Once thought to be a variant of FTC, HCC is now believed to be a distinctive category based on unique molecular studies and clinical outcomes. They are also sometimes referred to as oxyphilic thyroid carcinomas. HCCs typically present slightly later in life than other DTCs, between 50 and 60 years of age, but with the same 3:1 female preponderance.

Etiology
Hürthle cell carcinoma arises from Hürthle cells within the thyroid, thought to be related to follicular cells, which are large in size and produce thyroglobulin. By definition, these Hürthle cells must compose greater than 75% of a lesion for it to be considered HCC, and similar to FTC, the distinction between benign adenoma and carcinoma is made on histological identification of capsular or vascular invasion. No clear environmental causes...
or syndromes are associated with HCC, with sporadic mutation likely accounting for the majority of cases.21

**Note**

Hürthle cells must compose greater than 75% of a lesion for it to be considered HCC.

Presentation

Similar to other DTCs, HCC presents as either an asymptomatic palpable thyroid mass or is discovered incidentally on imaging. Despite its similarities to FTC, HCC presents more frequently with regional lymph node disease, which is present in nearly 20% of patients. Distant metastases are more common in HCC than with other DTCs and are present in approximately 30% of patients.22

Treatment

While initially thought to be much more aggressive than other DTCs, more recent literature, including a large database review, suggests a prognosis closer to PTC and FTC.20 Because of conflicting data, however, debate still surrounds the overall prognosis and no official guidelines exist on the management of HCC. Despite the controversy over prognosis, the general consensus is for completion thyroidectomy after diagnostic lobectomy. In contrast to the concerns for reliability of frozen section for diagnosing FTC, Maxwell et al recommend a treatment algorithm which relies on frozen section.19 There is no role for elective neck dissection, with therapeutic central and lateral neck dissection reserved for clinical node involvement in their respective compartments.

Adjunctive Therapies

Similar to surgical management, because of its low incidence and lack of large prospective studies, no true guidelines exist for adjuvant therapy of HCC. HCCs were previously thought to be poorly iodine avid and generally resistant to RAI therapy. A recent database review, however, by Jillard et al including more than 1,900 patients reported improved 5- and 10-year survival rates in patients with tumors greater than 2 cm and/or those with regional or distant metastases receiving postoperative RAI.23 In cases where HCC is not iodine avid, EBRT can be considered as an adjuvant therapy for advanced disease.

Variants

Recently a papillary variant of HCC has been identified resulting from a RET/PTC rearrangement, now referred to as Hürthle cell papillary thyroid carcinoma (HCPTC). HCPTC is generally thought to behave less aggressively than classic HCC. RET/PTC molecular testing is currently being used in some centers to help further risk stratify and guide treatment for benign Hürthle cell tumors.19

17.4.4 Staging and Prognosis of Differentiated Thyroid Carcinoma

The American Joint Committee on Cancer (AJCC) TNM staging guidelines are the same for all differentiated thyroid cancers. The primary tumor (T) component is based on the lesion size as well as the degree of extrathyroidal extension and local invasion. The regional lymph node (N) status is dependent on the presence or absence of regional lymph node metastases and in which compartment they occur (central [N1a] vs. lateral or mediastinal [N1b]). The distant metastasis (M) designation is based on the presence or absence of distant metastases (► Table 17.2). AJCC stage grouping guidelines are the same for all DTCs, with M stage critical for patients younger than 45 years and T, N, and M stages all contributing to patients 45 years and older (► Table 17.3).

**Table 17.2** American Joint Committee on Cancer (AJCC) TNM staging for thyroid carcinoma

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤ 1 cm, limited to the thyroid</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 1 cm but not &gt; 2 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm but not &gt; 4 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 4 cm in greatest dimension, limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease. Tumor invades the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease. Tumor invades prevertebral fascia or encases the carotid artery or mediastinal vessels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or superior mediastinal lymph nodes (level VII)</td>
</tr>
</tbody>
</table>

**Table 17.3** Distant metastasis classification (M)

<table>
<thead>
<tr>
<th>Distant metastasis classification (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

**Source:** Adapted from Edge et al.60

Notes: All anaplastic carcinomas are considered T4 tumors. The thyroid is composed of right and left lobes, with an isthmus connecting the two lobes.
The overall prognosis for DTC is very favorable, with 10-year survival rates approaching 90%. Survival rates diminish with increasing age (>45 years), tumor size (>4 cm), ETE, and the presence of distant metastasis. Accordingly, these factors are also the criteria for upstaging in the AJCC guidelines. Histology has also been found to be a prognostic factor for survival, with FTC, HCC, and variants of PTC (particularly tall cell) associated with decreased survival rates.

17.5 Medullary and Poorly Differentiated Thyroid Carcinomas

Medullary and poorly differentiated thyroid carcinomas (PDTCs), either by nature of their cells of origin or through dedifferentiation, do not possess the ability to concentrate or organify iodine, and in some cases do not have a functional p53 pathway for cell apoptosis. They are more aggressive than DTCs and have a worse prognosis.

17.5.1 Medullary Thyroid Carcinoma

Etiology

Medullary thyroid carcinoma arises from parafollicular C cells, which are derived from ultimobranchial body neural crest cells derived from the fourth branchial pouch. These cells migrate and join the thyroid gland in the upper, lateral lobes, which is where MTC occurs. MTCs secrete calcitonin and carcinoembryonic antigen (CEA), which are useful tumor markers in post-treatment surveillance. Approximately 50% of sporadic MTCs arise from somatic RET (RE-arranged during Transfection) oncogene mutations. Nearly all hereditary MTCs arise from autosomal dominant RET germline mutations.

Hereditary MTCs are classified based on disease phenotypes associated with specific RET mutations. They are grossly divided into two groups of syndromes: multiple endocrine neoplasia 2A (MEN2A) and MEN2B. MEN2A accounts for 95% of all hereditary MTCs. MEN2A is further subdivided into four groups: classic (MTC with pheochromocytoma and/or hyperparathyroidism), classic with cutaneous lichen amyloidosis, classic with Hirschsprung's disease, and familial MTC (classic without pheochromocytoma or hyperparathyroidism). In addition to MTC, the MEN2B phenotype includes pheochromocytoma (50%), skeletal abnormalities such as marfanoid habitus, ophthalmologic abnormalities, and mucosal ganglioneuromas, but lacks hyperparathyroidism.

Note: Hereditary medullary thyroid carcinoma is classified based on disease phenotypes associated with specific RET mutations.

Presentation

Sporadic MTC most commonly presents as an asymptomatic palpable thyroid mass or is discovered incidentally on imaging. Up to 70% of sporadic MTC patients have regional metastases and 10% have distant metastases at the time of diagnosis. Hereditary MTC may be diagnosed as the initial presentation of MEN2 or may be found during surveillance for patients from known MEN kindred. FNA is a reliable means for diagnosis of MTC and in cases when FNA findings are inconclusive or suggestive of MTC, FNA washout fluid can be measured for calcitonin levels to help clarify a diagnosis.

Treatment

Once the diagnosis of MTC has been made, preoperative serum calcitonin and CEA levels should be drawn. If calcitonin levels exceed 500 pg/mL, imaging to exclude metastatic disease should be performed. This includes contrasted CT scans of the neck and chest, three-phase contrasted multidetector CT or contrast-enhanced MRI of the liver; and MRI of the axial skeleton in conjunction with bone scintigraphy. PET scans are less sensitive and unfortunately no single imaging modality adequately provides whole-body surveillance for distant metastases.

Note: If calcitonin levels exceed 500 pg/mL, imaging to exclude metastatic disease should be performed.
All patients with presumed sporadic MTC should have direct DNA analysis for RET germline mutations to rule out hereditary forms. All patients with MTC should be screened for pheochromocytoma (plasma or 24-hour urine catecholamines and metanephrines or an adrenal CT) and hyperparathyroidism (calcium and parathyroid hormone [PTH]). If present, pheochromocytomas should be removed before thyroid surgery. Patients with hyperparathyroidism should undergo an appropriate parathyroid operation at the time of their thyroidectomy. In patients with MEN2A this may involve a total parathyroidectomy with or without reimplantation of a parathyroid remnant, a subtotal parathyroidectomy, or a selective removal of only pathologically enlarged glands guided by intraoperative PTH assessment.

ATA guidelines recommend a total thyroidectomy and bilateral central neck dissections for patients without clinical evidence of cervical lymph node disease and no evidence of distant metastases. Lateral neck dissection should only be performed in cases of clinically involved lymph nodes of the lateral compartment. No consensus could be reached with regards to the role of preoperative serum calcitonin levels influencing elective lateral neck dissection. Prophylactic thyroidectomy should be performed in the first months to years of life in patients with MEN2B (depending on the RET mutation) and at or before age 5 (based on serum calcitonin levels and RET mutation) for patients with MEN2A.25

**Adjunctive Therapies**

Since parafollicular C cells lack the ability to concentrate iodine, RAI has no role in the treatment for MTC. EBRT may be considered in patients with known persistent locoregional disease or those at high risk for recurrence (ETE or extensive lymph node metastases). Solitary distant metastases to the brain, lung, liver, or bone can also be considered for surgery, if feasible. Systemic therapy for distant disease has traditionally been reserved for palliation alone, though meaningful response rates are typically low. Currently, there are ongoing clinical trials studying the effects of tyrosine kinase inhibitors targeted at RET that may be considered for patients with advanced MTC.25

**Staging and Prognosis**

The AJCC TNM staging guidelines are the same for MTC as for patients older than 45 years with DTCs. Stage grouping guidelines from the AJCC, however, differ for MTC, with presence and location of regional metastasis, ETE, local invasion, and distant metastases all associated with a worse prognosis (∞ Table 17.4). Ten-year survival rates for patients with stages I, II, III, and IV disease are 100, 93, 71, and 21%, respectively.26

**Posttreatment Surveillance**

Serum calcitonin and CEA levels should be measured at 3 months after surgery. If undetectable or within normal range, they should be repeated every 6 months for 1 year, then yearly from then on. If postoperative serum calcitonin levels are elevated but less than 150 pg/mL, physical examination and US of the neck should be performed. If the results of these are negative, calcitonin, CEA, and neck US should be repeated every 6 months. If postoperative calcitonin levels are greater than 150 pg/mL, a more thorough imaging workup should be performed including neck US, a contrasted chest CT, contrasted MRI or three-phase contrasted CT of the liver, and bone scintigraphy with axial skeleton MRI. Surgery is recommended for any persistent or recurrent locoregional disease, in the absence of distant metastasis, and should include complete compartmental neck dissection for any biopsy- or image-positive lymph nodes.25

**17.5.2 Anaplastic Thyroid Carcinoma**

**Epidemiology**

Anaplastic thyroid carcinoma (ATC) accounts for approximately 3.6% of all thyroid carcinomas worldwide.27 It typically presents later in life, with an average age at diagnosis in the mid-60s; however, it does rarely affect patients in the late teens and early 20s. It is two to three times more likely to occur in women than men. Overall, ATC is one of the most aggressive and deadliest human solid tumors.

**Etiology**

Anaplastic thyroid carcinoma is thought to be a terminal dedifferentiation of carcinomas arising from thyroid follicular cells, namely PTC and FTC. Supporting this theory is the common association of PTC or FTC concurrently present in pathologic samples of ATC.

**Presentation**

Unlike other thyroid carcinomas, ATC most commonly presents as a rapidly growing neck mass, often in the background of a

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**Table 17.4 American Joint Committee on Cancer (AJCC) stage grouping for medullary and poorly differentiated thyroid carcinoma.**

<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IVA</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Source: Adapted from Edge et al.60
Carcinoma of the Thyroid

long-standing thyroid mass. Also, unlike other thyroid carcinomas, it is often associated with symptomatic neck pain, voice changes, respiratory obstruction, and/or dysphagia. Most ATCs are already at an advanced stage at the time of diagnosis. Invasion of local structures is common, 60% of patients have regional metastasis, and nearly 50% have distant metastatic disease. 

Rarely, it is diagnosed incidentally on histology as a small focus within a larger DTC. FNA can be diagnostic but may also yield nondiagnostic necrotic samples necessitating either core or open biopsy.

Note

Unlike other thyroid carcinomas, ATC most commonly presents as a rapidly growing neck mass, often in the background of a long-standing thyroid mass.

Treatment

Securing the diagnosis of ATC is critical for formulating any treatment plan. If the diagnosis is uncertain, open biopsy should be performed to confirm diagnosis. Once the diagnosis is confirmed, the ability to resect primary and regional disease should be determined by careful review of the imaging studies (US, CT, and/or MRI), and the presence of metastatic disease should be ruled out with PET.

The ATA guidelines recommend that in cases of incidentally noted ATC within lobectomy specimens, a completion thyroidectomy should be performed. For patients with completely intrathyroidal disease (only 10% of ATCs), total thyroidectomy with bilateral central and lateral neck dissections should be performed. For patients with ETE, if surgery is offered, then an en bloc resection should be performed with the goal of achieving grossly negative margins. Morbidity as the result of en bloc resection of disease invading adjacent structures should be considered and weighed against the improved survival benefit gained from gross negative margins. Aggressive surgical extirpations such as laryngectomy, tracheal resection, and cervical esophagectomy were previously discouraged in the 2012 ATA guidelines due to the increased morbidity without improved outcomes. A recent study in 2013, however, reported experience with 16 patients undergoing complete, aggressive surgical resections (including laryngectomy, tracheal resection, and cervical esophagectomy) with favorable outcomes in regard to both local control and overall survival, including 50% patient survival at mean follow-up of 4.8 years.

Debulking of unresectable tumor is discouraged due to lack of improvement in morbidity, local control, or survival. For unresectable disease, the role of tracheotomy or tracheal stenting for potential airway compromise, as well as feeding tube placement for enteral feeds and medication administration, should be discussed with the patient. Patients with unresectable disease should also be considered for palliative EBRT as it may enhance local control, prolong survival, improve quality of life, and prevent death from suffocation or exsanguination.

Patients with known metastatic disease, or who develop metastatic disease postoperatively, are not surgical candidates and may be appropriate for palliative EBRT and/or systemic therapy.

Given the very aggressive nature of ATC, associated poor prognosis, and high mortality, goals of therapy must be carefully discussed with the patient, and advanced directives are encouraged before proceeding with any treatment plan.

Note

A recent study demonstrated that complete, aggressive surgical resections resulted in favorable outcomes including a 50% patient survival at mean follow-up of 4.8 years in patients with anaplastic thyroid carcinoma.

Adjunctive Therapies

No adjunctive therapy is recommended for incidentally diagnosed intrathyroidal ATC. For all other ATC patients with negative margins or microscopic residual disease, good performance status, and no evidence of metastatic disease, postoperative EBRT in the form of intensity-modulated radiation therapy (IMRT) should be offered. Concurrent systemic therapy in the form of combination taxane and/or anthracyclines and/or a platinate agent should also be considered postoperatively, with close monitoring for neutropenia.

Staging and Prognosis

AJCC TNM staging guidelines for ATC are completely separate from all other thyroid carcinomas. All ATCs are considered T4, with ETE being the only distinguishing factor between T4a and T4b. Similarly, the AJCC group staging guidelines consider all ATCs stage IV, with ETE and distant metastasis conveying worse prognosis (see Table 17.5). Median survival is only about 5 to 6 months, with 1-year survival approaching 20%. Other poor prognostic factors include male sex and age more than 60 years.

Posttreatment Surveillance

Patients who desire continued aggressive management should have imaging of the brain, neck, chest, abdomen, and pelvis at 1- to 3-month intervals for up to 1 year, then repeated at 4- to 6-month intervals for at least an additional year. PET scan should be considered at 3 to 6 months after initial therapy and whenever there are clinical or radiographic findings suggestive of persistent, recurrent, or new distant metastatic disease. Surgical and/or palliative options should be discussed if recurrence is detected. Neither serum Tg measurements nor RAI scanning have a role in posttreatment surveillance for ATC.

Table 17.5 American Joint Committee on Cancer (AJCC) stage grouping for anaplastic carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T4a</th>
<th>T4b</th>
<th>Any T</th>
<th>Any N</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IVA</td>
<td>T4a</td>
<td>Any N</td>
<td>M0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td></td>
<td></td>
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Source: Adapted from Edge et al.
17.6 Other Carcinomas

17.6.1 Lymphoma

Primary thyroid lymphoma (PTL) is a rare form of thyroid carcinoma accounting for 1 to 3% of all thyroid malignancies. Most patients are diagnosed during the seventh and eighth decades of life, and there is a female preponderance of 3 to 4:1. There appears to be a strong association with Hashimoto’s thyroiditis, which imparts a 70- to 80-fold increased risk of developing PTL. Similar to ATC, PTL can present as a rapidly growing thyroid mass with symptoms of pain, voice changes, dyspnea, and dysphagia, in the setting of a long-standing goiter. Open biopsy is required for diagnosis and to rule out ATC. Tracheotomy, tracheal stent placement, and/or high-dose corticosteroids may be indicated to manage airway compromise. Treatment is nonsurgical, with combination EBRT and systemic (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone [CHOP]) therapy providing the best outcomes, with 5-year survival rates approaching 60%.33

17.6.2 Squamous Cell Carcinoma

Primary squamous cell carcinoma (PSCC) of the thyroid is very rare, comprising less than 1% of all thyroid malignancies with very few case reports in the literature. Metastatic SCC from the aerodigestive tract must be ruled out before this diagnosis can be made. PSCC typically presents as a rapidly growing thyroid mass with symptoms such as pain, dyspnea, and dysphagia. FNA is effective for diagnosis. Given the low incidence of PSCC, consensus treatment guidelines do not exist. Generally aggressive surgical treatment with total thyroidectomy and therapeutic central and lateral neck dissections are performed if the primary lesion is resectable. Adjuvant systemic and EBRT therapies have also been advocated. PSCC is very aggressive with a poor prognosis; median survival approaches less than 6 months.36

17.6.3 Metastatic Cancer

Metastases to the thyroid gland represent 1.4 to 3% of all thyroid carcinomas. Metastatic lesions commonly present in a delayed fashion with a mean latency of 53 months; this may be even longer in the case of renal cell carcinoma, which averages a 9.4-year interval between diagnoses. Rarely thyroid metastases are the first manifestation of a distant malignancy. Typically, metastatic thyroid malignancies present as asymptomatic palpable thyroid nodules, and less commonly as incidental imaging findings or symptomatic lesions. The most common primary tumor site is the kidney, followed by lung, head and neck, breast, and colon. Less commonly, they may originate from the esophagus, skin, stomach, neuroendocrine organs, and the ovary or uterus.34 The management depends on the presence of metastatic disease elsewhere in the body. If metastases are isolated to the thyroid gland, surgical resection is generally performed, with good potential for long-term survival, particularly in cases of metastatic renal cell carcinoma.35

17.7 Surgical Techniques

17.7.1 Conventional Open Thyroidectomy

The patient is positioned supine on the operating table with the neck gently extended to elevate the thyroid gland superiorly. A small degree of reverse Trendelenburg position of the operating table facilitates venous drainage during the surgery. General anesthesia is induced, and the patient is intubated. A laryngeal electromygographic endotracheal tube is used if laryngeal nerve monitoring is desired. This is best performed with a video laryngoscope so the surgeon can ensure correct placement of the laryngeal electrodes, and the anesthesia team should be counseled to avoid long-acting paralytic agents during induction.

The operative field is prepped and draped from sternal notch to chin, and from side-to-side to include lateral borders of the SCM to maximize orientation and exposure during the surgery. In performing concurrent lateral neck dissection(s), the superior border of the field should include the mastoid tip, jaw line, and lower lip to accommodate a larger incision and assist in identification of marginal mandibular branch of the facial nerve.

Planning of the incision must balance maintaining adequate exposure and the ability to deliver the gland with optimization of cosmetic outcomes. Much of this is dependent on the patient’s anatomy, the size of the thyroid gland, and the extent of surgery to be performed. Ideally, the thyroidectomy incision is placed in a natural skin crease about 2 to 3 cm above the sternal notch, approximately overlying the isthmus of the thyroid. This is best identified in the preoperative area while the patient is seated in an upright position, as this will best predict the resting place of the eventual scar. In younger patients lacking resting creases, slight neck flexion can help to produce a natural fold in the skin. If no such natural skin crease exists in the desired location, one should be made in the appropriate position parallel to a naturally occurring crease. The length of the incision will vary based on the size of the gland, but typically starts at 25 mm for small cancers and increases as needed. Incisions are extended superolaterally toward the mastoid tip, along the curve of a natural crease if present, for lateral neck dissection.

The incision is carried down through the platysma. Subplatysmal flaps are only raised if a lateral neck dissection is planned. The midline raphe between the strap muscles is identified and divided vertically. The sternohyoid and sternothyroid muscles are elevated off the underlying thyroid gland fascia with blunt dissection and retracted laterally. If any difficulty is encountered with dissection of the strap muscles off the gland, tumor extension into the strap muscles must be considered and en bloc resection of the muscle may be required. If exposure of the gland is inadequate secondary to the patient’s anatomy or due to the size of the thyroid gland itself, the strap muscles may be transected and later reapproximated without clinically significant loss of function. The sternothyroid muscle inserts along the oblique line of the lateral thyroid lamina and may obstruct visualization of the superior pole and pedicle. To improve access
to this area, the sternothyroid muscle may be divided along its line of insertion. Muscle reapproximation is unnecessary given that there is no functional deficit from this maneuver.

The order in which the following steps are taken to mobilize the thyroid gland may vary, with the ultimate goal to remove the thyroid while preserving parathyroid gland and RLN function. Only one such sequence is discussed in this chapter; however, the general concepts for each step remain the same regardless of the series in which they occur.

Attention is first directed toward mobilizing the superior pole. Isolation of the superior pedicle (containing both the superior thyroid artery and vein) is optimized with three maneuvers: atraumatic inferior retraction of the superior pole, superolateral retraction of the sternothyroid muscle with an angled retractor nearest to its attachment on the thyroid lamina, and dissection of an avascular cleft between the inferior constrictor muscles and dorsal aspect of the superior pole (referred to as Joll’s triangle), being careful to avoid injury to the SLN. As discussed above, transection of the sternothyroid muscle as it inserts along the thyroid lamina can also be performed to further assist in exposure.

The external branch of the SLN typically separates itself from the course of the vascular pedicle about 1 cm above the superior pole, and dives deep as it continues along its path to the cricothyroid muscle on the surface of the inferior constrictor muscle. Attempts should be made to identify the SLN before dividing the upper pedicle. This may not be possible 20% of the time when the SLN travels within the inferior constrictor muscle. Stimulation of the inferior constrictor muscle with movement of the cricothyroid muscle may reveal an intramuscular course of the nerve.40

The upper pedicle is divided with an advanced energy device, and then the superior parathyroid gland is typically found on the dorsal aspect of the mid- to upper thyroid gland. Once identified, dissection of the superficial fascia (false capsule) off the thyroid gland beginning ventral (or more anterior) to the parathyroid gland should be performed. This will allow the parathyroid gland to be swept off of the thyroid while preserving its blood supply. The remainder of the superior pole can then be dissected along the same plane until it is freely mobile and can be retracted inferiorly and medially. Inspection for a pyramidal lobe should also be performed at this time.

As the thyroid gland is released further medially and begins to roll over the trachea, exposure of the posterolateral aspect of the gland improves. This aids in the detection of the inferior parathyroid gland, which is typically located on the posterior aspect of the mid to lower lobe. Once identified, the superficial fascia ventral to this location is dissected off the true thyroid capsule and the parathyroid gland is dissected inferolaterally, preserving its blood supply. The remainder of the inferior pole can then be dissected free along a similar plane further assisting in medial retraction of the lobe.

Attention is then focused on identifying the RLN, which is identified just proximal to the ligament of Berry and using the tubercle of Zuckerkandl as a landmark. It is worth noting that the right RLN runs obliquely across the central neck compartment in a superomedial direction toward the cricothyroid joint, while the left RLN takes a more vertical path along the tracheoesophageal groove. Gentle dissection should be performed perpendicular to the course of the nerve while maintaining concurrent counterretraction on the thyroid gland medially and the strap muscles/cariotid artery laterally. The RLN is non-recurrent on the right in up to 1.6% of patients. In these rare cases, the RLN takes a more direct horizontal route from the vagus nerve toward the cricothyroid joint.

Once identified, the distal segment of the RLN may then be traced until it courses under the inferior constrictor muscle. The RLN has extralaryngeal branches in up to 60% of patients. When identified, each branch of the RLN should be preserved, especially the most anterior branch which usually provides most of the laryngeal innervation. Once the thyroid lobe and Berry’s ligament are completely free from the RLN, dissection of Berry’s ligament continues medially along the pretracheal fascia deep to the isthmus. At this point the isthmus may be divided to complete a lobectomy or attention may be turned to the contralateral lobe and the above steps are repeated for a total thyroidectomy.

After irrigating the wound bed and achieving hemostasis, the parathyroid glands should be inspected for viability and intact vascular supply. If they appear visibly compromised, autotransplantation into the SCM or a strap muscle should be considered. If the strap muscles were divided earlier in the procedure, they may be reapproximated at this time. To prevent skin tethering to the trachea, the strap muscles may be reapproximated along their midline in slender individuals. This is performed with a single figure-of-eight absorbable suture, which allows a wide area for the egress of blood from the deep neck into the subcutaneous space (Fig. 17.6). This technique prevents the hydrostatic lymphovenous compression that can result in fatal airway obstruction in the event of a postoperative hematoma (for this reason, in most patients the strap muscles are not closed at all). Drains are not necessary in central compartment surgery unless the patient will be on postoperative anticoagulation (e.g., dialysis patients). Before closing the wound, a small sliver of the skin edge can be trimmed using sharp iris scissors to allow for more predictable wound healing and decreased risk of hypertrophic scarring.

17.7.2 Minimally Invasive Thyroidectomy and Minimally Invasive Video-Assisted Thyroidectomy

Minimally invasive thyroidectomy (MITH) has been proven to be a safe and effective option for many patients, including those with thyroid carcinomas.41,42 Indications for MITH include low-risk DTCs with nodule size less than 5 cm, in the absence of locally advanced, metastatic, or recurrent disease. Incisions as small as 25 to 30 mm may be used to gain access to the thyroid compartment. Avoidance of subplatysmal flaps, liberal use of advanced energy devices, and carefully placed retraction provides ample exposure to identify and preserve the recurrent
nerves and parathyroid glands, while also accomplishing a thorough and oncologic thyroidectomy.

Minimally invasive video-assisted thyroidectomy (MIVAT) employs endoscopes to further reduce the incision size and extent of dissection. Miccoli et al have refined this technique and reported extensively on its safety and efficacy, including its use for thyroid carcinoma.\(^4\) The surgery is a three-part procedure, starting with an open technique, followed by the endoscopic component, then completed in an open fashion. The surgery starts with a 15- to 20-mm incision through the skin down to the strap muscles. The platysma, which is typically absent in the midline, is either not exposed or divided as necessary. The midline raphe is opened and the strap muscles are then bluntly dissected off the thyroid gland. The middle thyroid vein is ligated allowing for retraction of the thyroid gland over the trachea. The endoscopic component proceeds with use of a 5-mm 30-degree endoscope angled upward to visualize the superior pole. Retractors are used to distract the strap muscles laterally and the thyroid gland medially. A small amount of the sternothyroid muscle may be divided near its insertion on the thyroid lamina to improve visualization of the superior pedicle. The pedicle is then isolated and ligated with ultrasonic shears, taking care not to injure the SLN (\(\triangleright\) Fig. 17.7). The remainder of the superior pole is released and the superior parathyroid gland is identified and preserved as previously described. The endoscope is next angled inferiorly and the inferior pole is dissected free to allow further medial retraction of the thyroid lobe. The RLN is identified (\(\triangleright\) Fig. 17.8) and the inferior parathyroid gland preserved.

**Note**

Minimally invasive video-assisted thyroidectomy employs endoscopes to further reduce the incision size and extent of dissection.

Removal of the gland requires return to open surgery. The superior lobe is first delivered through the wound using medium-sized clamps sequentially placed on the gland as it is delivered. Any remaining attachments superiorly are lysed at this time. The remainder of the gland is then delivered through the wound. Once completely delivered, the lobe is retracted medially and the RLN is traced to its laryngeal entry point. The remainder of Berry’s ligament is released. The isthmus is then divided close to the contralateral lobe. This either completes the lobectomy or attention is next directed to the contralateral lobe, which is removed to accomplish a total thyroidectomy.\(^4\)\(^1\),\(^4\)\(^2\) Indications for MIVAT in thyroid carcinomas include low-risk DTCs with nodule size less than 3 cm, the absence of locally advanced, metastatic, or recurrent disease, and no thyroiditis or substernal extension.
17.7.3 Remote Access Thyroid Surgery

Remote access thyroid surgery involves removal of the thyroid gland without an incision on the visible portion of the anterior neck. This may be achieved via endoscopic- or robotic-assisted surgical techniques. The two most commonly performed remote access procedures in the United States are the transaxillary and postauricular facelift techniques. While shown to be safe and effective in appropriately selected patients, limited data are available on the use of remote access surgery for thyroid cancer outside of South Korea. The indications for its use in thyroid cancer surgery in the United States are extremely limited, including patients desiring to avoid a neck incision with small DTC, without locally advanced, metastatic, or recurrent disease.45

17.7.4 Central Neck Dissection

The central neck compartment consists of levels VI and VII lymph nodes (Fig. 17.9), and is bounded by the hyoid bone superiorly, the level of the innominate artery inferiorly, the carotid arteries laterally, the prevertebral fascia posteriorly, and the undersurface of the sternothyroid muscles anteriorly. Levels VI and VII nodes are separated by the sternal notch. The 2009 ATA consensus statement on CND for thyroid cancer divided the central neck into four surgically relevant compartments: prelaryngeal (also known as Delphian), pretracheal, and left and right paratracheal.46 Comprehensive, compartment-oriented removal should be performed when central neck dissection is indicated, and so-called berry picking of only clinically involved lymph nodes is not recommended (Fig. 17.10).

Prelaryngeal dissection may be performed during resection of a pyramidal lobe or after thyroidectomy. Nodal tissue is dissected in a step-wise fashion from the superior margin of the isthmus, upward over the cricoid cartilage and cricothyroid membrane, and then onto the anterior surface of the thyroid cartilage up to the hyoid bone. The perichondrium of the respective cartilages should be preserved. Special care must be paid to the cricothyroid muscle as it is very thin and injury can cause vocal dysfunction.

Pretracheal dissection starts at the inferior aspect of the isthmus and involves removing the fibrofatty contents overlying the anterior trachea down to the level of the innominate artery. Delineating the most inferior border can be helped by digitally palpatating for the innominate artery. When approaching the inferior boundary of dissection, the more ventrally located brachiocephalic vein must be located and avoided. Feeding vessels to the pretracheal lymph nodes have the potential to be large and should be ligated securely.

The rectangular-shaped paratracheal regions are bounded superiorly by the level of the cricoid cartilage, inferiorly by the intersection of the innominate artery and the trachea, laterally by the carotid artery, and medially by the trachea. To preserve the parathyroid glands and their vascular supply, the inferior glands should be identified before initiating dissection and swept gently away from the paratracheal region along with the ITA. If this is not possible, the inferior parathyroid glands may be removed and autotransplanted into an appropriate recipient.
muscle after confirming its identity with frozen section. Since the superior parathyroid glands are usually located superior to the cricoid cartilage, they are at lower risk for injury.

Initial paratracheal dissection involves opening the carotid sheath from the level of the thyroid cartilage down to the level of the innominate artery, thereby establishing the lateral border of dissection. Identification of the vagus nerve within the carotid sheath aids in stimulation and assessment of RLN integrity. During dissection, it is helpful to retract the laryngotracheal complex medially to expand exposure of the paratracheal region. The entire course of the RLN is next dissected from its point of laryngeal entry, down toward the mediastinum where it emerges from behind the carotid artery. The rectangular-shaped right paratracheal region is grossly divided by the oblique course of the RLN into two triangles (▶ Fig. 17.11). Dissection of the nerve should be performed with minimal manipulation, avoiding the use of a nerve hook and thermal injury from cautery.

The fibrofatty contents of the left paratracheal region are removed as a single specimen by dissecting the tissue off the prevertebral fascia posteriorly, the esophageal muscularis, and trachea medially. Again, caution should be exercised when defining the inferior boundary of the dissection near the great vessels. Careful hemostasis is achieved after irrigation and Valsalva maneuver. CND does not necessitate placing a drain.

### 17.7.5 Lateral Neck Dissection

Metastasis to the lateral neck compartment can occur in levels II to V, with level IV being the most common site. Level I is rarely involved, usually only occurring in aggressive malignancies with concurrent nodal disease in level II. The ATA consensus review of lateral neck dissection for DTC in 2012 recommends selective neck dissection of levels IIA, III, IV, and V when clinically indicated. Furthermore, this should be performed in a comprehensive manner and so-called berry picking of only clinically involved lymph nodes is strongly discouraged. The surgical technique for lateral neck dissection is addressed in other chapters of this book.

<table>
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<tr>
<td>Level I is rarely involved, usually only occurring in aggressive malignancies with concurrent nodal disease in level II.</td>
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</table>
17.8 Complications of Thyroid Surgery

17.8.1 Postoperative Hematoma

Hematoma following thyroid surgery is rare, occurring in fewer than 2% of patients. When it does occur, however, it can cause life-threatening airway obstruction. Meticulous hemostasis should be maintained during surgery. Irrigation and a Valsalva maneuver may be performed to provoke indolent sites of bleeding. The most important maneuver to minimize the likelihood of catastrophic outcomes, however, is loose (or no) closure of the strap muscles so that blood or fluid can escape into the subcutaneous tissue rather than causing lymphovenous compression and supraglottic edema. Deep extubation should be performed when possible to prevent excessive coughing and bucking on emergence. Perioperative emetics may also be administered when indicated to decrease the risk of postoperative nausea and vomiting. The prophylactic use of drains does not affect the rate of postoperative hematoma formation.

**Note**

Prior to wound closure, wound irrigation and a Valsalva maneuver may be performed to provoke indolent sites of bleeding.

Small asymptomatic fluid collections may be observed at the discretion of the surgeon. When symptomatic hematoma formation is appreciated, the wound should be opened at the bedside to relieve pressure and prevent airway compromise. The patient is then returned to the operating room for evacuation of the hematoma, exploration of the wound, and control of bleeding.

17.8.2 Recurrent Laryngeal Nerve Injury

True rates of RLN injury are difficult to appreciate without universal standardized protocols for detecting palsy (e.g., routine pre- and postoperative laryngoscopy), which probably leads to underreporting. Published rates of RLN injury range from 2.5 to 18.6%. While these data are derived from expert surgeons in high-volume centers, up to 50% of thyroid surgeries in the United States are performed by surgeons who perform five or fewer operations annually, suggesting that true rates of RLN injury are likely to be substantially higher than the published data suggest.

Injury to the RLN may be transient or permanent, with many cases of transient injury possibly going unnoticed by the patient and surgeon if postoperative laryngoscopy is never performed. RLN injury may result in breathy voice, aphonia, aspiration, or dyspnea; bilateral paralysis may result in stridor and life-threatening airway compromise necessitating an artificial airway.

**Note**

Injury to the RLN may be transient or permanent, with many cases of transient injury possibly going unnoticed by the patient and surgeon if postoperative laryngoscopy is never performed.

If a transected nerve is recognized during surgery, primary neurorrhaphy is recommended. Alternatively, an ansa cervicalis–RLN anastomosis or cable grafting of longer segments of injured/missing nerve may be performed. For symptomatic paresis, vocal fold medialization may be performed as a temporary intervention. In cases of permanent symptomatic paralysis, vocal fold injection with long-lasting materials (especially autologous fat), thyroplasty (with or without arytenoid adduction), and/or reinnervation with ansa cervicalis nerve are all options.

**Note**

If a transected nerve is recognized during surgery, primary neurorrhaphy is recommended.

17.8.3 Superior Laryngeal Nerve Injury

Injury to the external branch of the SLN may occur in up to 58% of patients, most commonly during dissection of the superior thyroid vessels. Injury to this nerve results in dysfunction of the cricothyroid muscle, which manifests in a diminished vocal range and decreased vocal projection. SLN injury can be minimized by identifying the nerve during isolation of the superior pedicle, gentle manipulation to sweep the nerve away if needed, and judicious use of cautery when in its proximity.
17.8.4 Hypoparathyroidism

Hypoparathyroidism is the most common complication after thyroid surgery. Temporary hypoparathyroidism (lasting ≤6 months) occurs in 10 to 15% of patients, while permanent hypoparathyroidism (>6 months) occurs in 1 to 3% of patients. The risk of hypoparathyroidism increases with the extent of surgery being performed, surgery for cancer, reoperations, and concurrent central neck dissection. Hypoparathyroidism may be the result of direct trauma, accidental removal, or indirect revascularization of the parathyroid glands. The thyroid specimen should be closely inspected for retained parathyroid tissue. Auto-transplantation should be considered for all parathyroid glands that appear to have compromised vasculature or that were removed inadvertently.

**Note**

Hypoparathyroidism is the most common complication after thyroid surgery.

Signs and symptoms of hypoparathyroidism include perioral numbness/tingling, muscle cramping, tetany, Chvostek’s and Trousseau’s signs, and a prolonged QT interval. While postoperative calcium and PTH levels may be drawn to help dictate treatment for and/or predict development of hypoparathyroidism, an empiric tapering dose of calcium and vitamin D postoperatively has been shown to be a cost-effective way of minimizing symptomatic hypocalcemia after total or completion thyroidectomy.

17.9 Clinical Cases

17.9.1 Case 1: T4aN1bM0 Papillary Thyroid Carcinoma with Tracheal Invasion

**Clinical Presentation**

A 58-year-old Caucasian woman presented to her physician with a 6-month history of bright red hemoptysis. She denied any dyspnea, dysphagia, pain, or cervical masses. She had no history of radiation exposure and no family history of thyroid disease. She had a known thyroid nodule that was biopsied 6 years previously, but the specimen was inadequate and she had no further follow-up. A CT scan showed a right thyroid mass with tracheal invasion (Fig. 17.13) and she was referred for specialty care.

**Physical Examination**

Her voice was normal, and she had no dyspnea or stridor. Palpable enlargement of the right thyroid was present, with no discrete nodules. There was no appreciable pathologic lymphadenopathy. US revealed a large, irregular hypoechoic mass in the medial aspect of the right thyroid with no distinct borders and no clear tracheal margin. In-office flexible laryngoscopy and tracheoscopy revealed a mucosalized mass extending into 60% of the tracheal lumen, starting just below the cricoid cartilage (Fig. 17.14). The distal airway was clear. She had normal bilateral vocal fold mobility.

**Diagnosis and Workup**

The patient’s presentation was concerning for an aggressive thyroid malignancy with airway invasion. FNA of the right thyroid mass was suspicious for malignancy. There were no features suggestive of anaplastic carcinoma and calcitonin staining was negative. The serum calcitonin was normal. A CT of the chest was unremarkable.

**Options for Treatment**

The patient was discussed at the multidisciplinary endocrine tumor conference, and the recommendation was made for the laryngology and head and neck endocrine surgery team to perform an esophagoscopy, total thyroidectomy, CND, right lateral neck dissection, resection of the involved trachea, and airway reconstruction. Potential tracheal reconstruction options considered included a pedicled muscle flap, thyroid or rib cartilage grafting, or tracheal resection and reanastomosis.
Treatment

The patient was taken to the operating room for a rigid esophagoscopy, total thyroidectomy, bilateral CND, right lateral neck dissection levels IIA through V, and resection of the involved portion of the trachea. There was no esophageal invasion. The right lateral neck dissection was performed first. The thyroid was completely mobilized except for where the tumor had penetrated the anterolateral right tracheal wall. During this process, both RLNs were identified and preserved. The bilateral CNDs were then performed. Attention was then turned to the tracheal resection.

A no. 15 blade was used to incise the trachea around the location of the tracheal invasion. The inferior aspect of the cricoid cartilage was incised, but the cricoid ring was left intact. Approximately 50% of the right and anterior aspects of the first, second, and third tracheal rings resected, allowing removal of the invasive tracheal portion of the tumor en bloc with the total thyroidectomy specimen. This resection was accomplished while maintaining the anatomical integrity of the RLNs. Stimulation of the bilateral RLNs after tumor resection demonstrated normal bilateral responses. The transoral endotracheal tube was withdrawn and a 6.0-mm endotracheal tube was placed into the distal trachea (▶ Fig. 17.15).

Because of the extent of the tracheal resection required, tracheal reconstruction began by resecting the remaining portions of the second and third tracheal rings. This allowed the distal trachea to be anastomosed to the first tracheal ring on the left, and a thyroid alar cartilage graft to be used to fill the defect on the right. A suprathyroid tracheal releasing maneuver was performed. A 15 x 7 mm thyroid alar cartilage graft was harvested, leaving the inferior border of the thyroid cartilage and inner thyroid cartilage perichondrium intact. The distal trachea was then sutured to the thyroid cartilage with internal Grillo’s stitches. A tracheostomy was made two rings below the defect, and the endotracheal tube was replaced through this incision. The tensionless tracheal anastomosis was then completed, and the thyroid cartilage graft was sutured over the defect in the right trachea (▶ Fig. 17.16). A sternohyoid muscle flap was placed over the reconstruction. The wound was closed and the endotracheal tube was replaced with a tracheostomy tube over a guidewire. External Grillo’s sutures were placed. She was discharged from the hospital on postoperative day 4. Her final pathology showed a 2.9-cm follicular variant PTC with extensive lymphovascular and extrathyroidal invasion, as well as extranodal extension. She was staged as T4aN1bM0.

On postoperative day 10, she returned to the operating room for an airway examination. This showed an intact anastomosis
with minimal stenosis and granulation tissue, which was treated with a microdebrider and balloon dilation (▶ Fig. 17.17). She was decannulated that day without difficulty. Postoperative laryngoscopy revealed mild right vocal fold weakness, which resolved after 9 months, resulting in a normal voice. She received 152 mCi of 131I 2 months after surgery. One year after treatment, her neck US and whole-body scan were negative for recurrent disease, and her Tg was 1 ng/mL with undetectable Tg antibodies. She continues to have regular follow-up with endocrinology and otolaryngology specialists.

17.9.2 Case 2: T2N1bM0 Medullary Thyroid Carcinoma

Clinical Presentation

A 50-year-old Hispanic man presented to the emergency room with a 3-month history of enlarging, tender, left-sided cervical lymphadenopathy, which had not improved after 2 weeks of antibiotic therapy. He had no history of head and neck radiation, no history of tobacco or alcohol use, and no known family history of thyroid cancer. He had left otalgia but no dysphonia, dysphagia, odynophagia, or hemoptysis. He was uninsured and had been receiving all his medical care through the emergency department.

Physical Examination

The otolaryngology service evaluated the patient and noted a firm left thyroid mass and multiple hard, tender, fixed, enlarged left cervical nodes, the largest measuring 3 × 5 cm. No other head and neck lesions were noted. Flexible laryngoscopy demonstrated normal bilateral vocal fold mobility.

Diagnosis and Workup

Based on the findings a CT scan of the neck and FNA of the largest left cervical node were performed. The CT showed a left thyroid mass and multiple enlarged nodes in the left lateral neck (▶ Fig. 17.18). The FNA revealed a poorly differentiated carcinoma. Immunohistochemistry markers for SCC were negative. The specimen was positive for thyroid transcription factor 1, calcitonin, and CEA, and negative for Tg. These findings were consistent with medullary thyroid carcinoma. His serum calcitonin was 4,645 pg/mL (normal < 5 pg/mL) with a CEA of 414 ng/mL (normal ≤ 5 ng/mL). There was no evidence of distant metastases on CT of the chest or abdomen and urinary studies for metanephrines and catecholamines were negative. He could not afford RET testing. He was staged as T2N1bM0.

Options for Treatment

The diagnosis of MTC with metastases to cervical nodes was discussed with the patient. He was counseled that although his disease was incurable (< 10% given his nodal burden), surgery was recommended to reduce his disease burden, improve his symptoms, and decrease the risk to surrounding structures. Given his imaging findings and calcitonin level greater than 200 pg/mL, total thyroidectomy, CND, and bilateral lateral neck dissection were recommended. He was also evaluated by an oncologist and was determined not to be a candidate for systemic therapy with a tyrosine kinase inhibitor given the lack of distant metastases.
Treatment

The patient underwent an uncomplicated total thyroidectomy, bilateral CND, and bilateral lateral neck dissection levels IIA, III, IV, and V. Postoperatively, his calcitonin and CEA decreased to 33.2 pg/mL and 2.72 ng/mL, respectively. He was followed every 3 months by otolaryngologist and endocrinologist. Two years after surgery, he developed a new tender posterior left cervical node. His calcitonin increased to 190 pg/mL and the CEA rose to 13.9 ng/mL. FNA of the node revealed recurrent MTC. A postoperative bilateral CND, and bilateral lateral neck dissection levels IIA, III, IV, and V. Postoperatively, his calcitonin and CEA decreased to 26 pg/mL and 2.6 ng/mL, respectively. He continues to be followed every 3 months.

References


18 Carcinoma of the Salivary Glands

Mark K. Wax and Savannah G. Weedman

18.1 Introduction to Salivary Gland Carcinoma

Salivary gland cancers are the most diverse head and neck neoplasms with a wide range of histological subtypes, and widely varying biological behavior within those subtypes. These often do not subscribe to commonly used histological grading systems. Given these variations, the classification systems and terminology are continually evolving. Salivary gland cancers are also relatively uncommon, making up less than 5 to 8% of all primary head and neck cancers. Each of these factors makes outcome comparisons between studies, prediction of clinical course of disease, and treatment consensus for these cancers very difficult.

The primary treatment modality continues to be surgery, with adjuvant radiotherapy when adverse pathologic features are found. Chemotherapy has thus far not been shown to be beneficial in the treatment of salivary gland cancer. A fair amount of progress has been made in the realm of genetics and immunotherapy for the treatment of salivary gland cancers over the past decade, and many clinical trials are examining the efficacy of targeted therapies on outcomes for salivary gland malignancies. Further research must be done before incorporating targeted therapies in treatment recommendations.

This chapter focuses on malignant carcinoma of the major salivary glands. Minor salivary gland cancer treatment and the remainder of the head and neck follow the paradigm of other carcinomas in these regions, with the exception of differences in chemotherapeutic and immunotherapeutic adjuvant treatment, which we do not discuss.

18.2 Epidemiology

Cancer of the salivary glands is rare accounting for up to 0.9% of all cancers in the United States according to the 2009 National Cancer Database Report. The incidence of primary major salivary gland cancer according to the most recent U.S. Surveillance, Epidemiology, and End-Results (SEER) data is 1.3 per 100,000 people per year with a mean age at the time of diagnosis of 60 years with no gender prevalence. The incidence of salivary gland cancer has increased by an average of 0.6% per year, slightly faster in males than females, from 2006 to 2012.

Salivary gland cancers can be broadly divided into epithelial and nonepithelial, or mesenchymal lesions. Epithelial-derived salivary malignancies are far more common than those that are nonepithelial. The majority, 70%, of these have been shown to arise from the parotid gland, 8% from the submandibular gland, and 22% from seromucinous glands in the upper aerodigestive tract. Among malignant epithelial tumors, or carcinomas, mucoepidermoid carcinoma (MEC) was previously the most common, accounting for nearly 15% of all tumors, followed by adenoid cystic carcinoma (ACC), adenocarcinoma, and malignant mixed tumor. In the more recent U.S. SEER data report, adenocarcinoma was the most common major salivary gland cancer, accounting for over half of all salivary gland carcinomas. Data from the Netherlands showed ACC was the most common salivary gland malignancy using the 1972 WHO classification.

Mesenchymal tumors are histologically very diverse and make up only 2 to 5% of all salivary gland tumors. A recent literature review from 1990 to 2010 found a total of 187 cases of malignant mesenchymal salivary gland tumors and identified 42 different histological diagnoses. Primary tumor location for malignant mesenchymal major salivary gland tumors is approximately 80% parotid gland, 15% submandibular gland, and 1% sublingual gland.

18.3 Etiology

The etiology of carcinoma of the salivary glands is believed to be multifactorial. A combination of environmental factors as well as certain genetic abnormalities may contribute to the development of a carcinoma in one of the salivary glands (Table 18.1).

Tumors of the salivary glands represent a diverse class of neoplasms whose biological aggressiveness ranges from indolent to aggressive. Unlike epidermoid carcinoma, the etiology of carcinoma of the salivary gland is unclear. Tobacco and alcohol have not been implicated in the development of salivary gland neoplasms; however, radiation has been implicated as a possible contributing factor.

As with other endocrine and solid organ tumors of the head and neck, ionizing radiation has been shown to increase the risk for the development of carcinoma in the salivary glands. Patients who are exposed to radiation have been shown to be more prone to the development of both benign and malignant salivary gland tumors. Data accumulated over time have demonstrated that patients who have received radiation therapy for
head and neck cancer have a 4.5-fold incidence of developing a salivary tumor within 11 years of treatment, and MEC is the most predominant type.\textsuperscript{3,11}

There is some evidence to suggest that exposure to silica dust can cause an increased risk of cancer in the salivary glands. Other factors such as a history of early menarche and multiparity may also contribute to an increased risk. Several studies have examined the role of Epstein–Barr virus in the development of certain types of salivary gland tumors. Whether this is because of the high prevalence of Epstein–Barr virus in these patient populations is unknown.

Given that dietary factors have been linked to numerous other cancers, these have been studied in salivary cancer for causative and preventative effects. Vegetables (particularly yellow and orange), vitamin C intake greater than 200 mg/day, liver, and fiber have each independently been associated with a statistically significant decreased risk of salivary gland cancer, so may have some protective effect.\textsuperscript{12,13} Only cholesterol intake has been found to be statistically significantly associated with an increased risk of salivary gland cancer.

Evaluation of the SEER database from 1973 to 2011 showed an increased incidence of salivary gland carcinoma among patients with a previous index cancer; these results were consistent even when excluding patients whose index cancer was in the head and neck.

### Table 18.1 Factors that may contribute to the development of salivary carcinoma

| Environmental       | \n|---------------------|
| Radiation           |
| Ionizing            |
| Subtherapeutic      |
| Hazardous nuclear plant exposure |
| Ultraviolet light  |
| Dietary             |
| High intake of polyunsaturated fats |
| Silica dust exposure |
| Hormonal            |
| Early menarche      |
| Multiparity         |
| Viral               |
| Epstein–Barr virus  |
| Genetic             |
| Allelic loss        |
| Structural rearrangement |
| Monosomy/polysomy  |

18.4 Anatomy of the Salivary Glands

The salivary glandular system is composed of three pairs of major salivary glands (the parotid, submandibular, and sublingual glands) and 700 to 1,000 minor salivary glands that are spread throughout the upper aerodigestive tract lining but concentrated in the oral cavity and oropharynx (Fig. 18.1).

#### 18.4.1 Embryology

The major salivary glands arise from oral ectoderm outpouchings into the endoderm beginning around the seventh week of gestation. Acinar cells form secretory end pieces and produce saliva which is modified while passing through a series of ductal structures before emptying into the oral cavity via the excretory duct. The extracellular matrix is made up of myoepithelial cells, myofibroblasts, immune cells, endothelial cells, stromal cells, and nerve fibers. The internal anatomy of each major salivary gland is fairly similar with the exception of the parotid gland and its unique relationship with the facial nerve and the nearby lymphatics. During development, as the gland grows posteriorly, the facial nerve grows anteriorly, until the gland surrounds the nerve. The parotid gland capsule also forms later than the others after lymphatic development, resulting in the entrapment of lymph tissue within the capsule. The minor salivary glands develop later from both oral ectoderm and nasopharyngeal endoderm.

#### 18.4.2 Parotid Gland

The parotid gland is the largest of the major salivary glands. The body of the gland lies over the ramus of the mandible and the masseter muscle. The inferior aspect of the gland, known as the tail of the parotid, descends into the upper neck. The parotid fascia, or capsule, is continuous with the superficial layer of the deep cervical fascia. The superficial layer is continuous with the sternocleidomastoid (SCM) muscle, masseter, and zygoma. The deep layer extends from the fascia of the posterior belly of the digastric and forms the stylomandibular membrane, separating the parotid and submandibular glands.

The stylomandibular tunnel serves as a conduit connecting the deep and superficial lobes of the parotid gland. The deep lobe passes through the stylomandibular tunnel and extends into the prestyloid compartment of the parapharyngeal space (Fig. 18.2). Tumors arising within the deep lobe of the parotid gland develop medial to the mandible in the prestyloid compartment of the parapharyngeal space, because the parotid tissue can herniate through the stylomandibular membrane (Fig. 18.3). These tumors not uncommonly present with an oropharyngeal component.

Although there is no fascial separation between the deep and superficial lobes of the parotid gland, the facial nerve and the retromandibular vein are used as anatomical markers between the lobes. Within the parotid gland, the facial nerve divides into two or three main trunks at pes anserinus and becomes more superficial as it travels anteriorly through the gland. The lower...
The auriculotemporal nerve parallels the superficial temporal artery and vein; it provides postganglionic parasympathetic innervation from the otic ganglion to the parotid gland, and carries sensory input from the parotid capsule, temporal skin, and auricular skin.

Arterial supply to the parotid comes from the transverse facial artery, arising from the superficial temporal artery. The retro-mandibular vein drains the parotid; it runs through the gland deep to the facial nerve, exits at the inferior pole and joins both the postauricular vein to form the external jugular vein, and the anterior facial vein to form the common facial vein.

Parotid lymphatics eventually drain into the cervical lymph nodes and include the paraparotid nodes, and the less numerous intraparotid nodes. Paraparotid lymph nodes drain the...
temporal region, scalp, and auricle; intraparotid nodes drain the ear, soft palate, and posterior nasopharynx.

Saliva drains into the oral cavity via the parotid duct (Stenson's duct), which is approximately 5 cm long, 5 mm in diameter, and runs with the buccal branch of cranial nerve (CN) VII, approximately 1.5 cm inferior and parallel to the zygomatic arch. Stenson's duct pierces the buccinator to empty into the oral cavity at the parotid papilla, adjacent to the first or second maxillary molar.14

Note
Parotid lymphatics drain into the upper cervical lymph nodes and include the paraparotid nodes, and the less numerous intraparotid nodes.

18.4.3 Submandibular Gland
The submandibular gland sits in the submandibular triangle and has superficial and deep lobes which are contiguous. The deep portion of the gland extends around the free posterior border of the mylohyoid muscle; this deep lobe comprises the majority of the gland. The fascia, or capsule, of the submandibular gland is also contiguous with the superficial layer of the deep cervical fascia.

The gland is intimately related to the lingual nerve and ganglion, which provides parasympathetic innervation to the gland. The marginal mandibular nerve crosses superficial to the facial vein along the anterior aspect of the glandular capsule.

Sympathetic innervation travels via the lingual artery from the superior cervical ganglion. Parasympathetic innervation travels from the submandibular ganglion to the gland via the lingual nerve.

Vascular inflow and outflow are via branches of the facial artery and facial (or anterior facial) vein. The facial artery courses in a groove on the deep part of the gland and passes through the gland capsule before reaching the mandible. The anterior facial vein courses superficial to the gland before the artery and vein meet and run over the inferior border of the mandible.

Lymphatic drainage is via the deep cervical and jugular chains of nodes. The perifacial nodes are often involved in primary submandibular gland cancer and should be removed with the specimen.

The submandibular duct (Wharton's duct) is about 5 cm. It exits the medial side of the gland and runs between the mylohyoid and hyoglossus muscles, then onto the genioglossus muscle. It runs parallel and just superior to CN XII and is in
Carcinoma of the Salivary Glands

close association with the lingual nerve. Wharton’s duct starts medial and ends lateral to the lingual nerve. It empties into the oral cavity at the lingual caruncle, in the anterior floor of mouth adjacent to the frenulum.14

Note

lymphatic drainage is via the deep cervical and jugular chains of nodes. The perifacial nodes are often involved in primary submandibular gland cancer and should be removed with the specimen.

18.4.4 Sublingual Gland

The sublingual glands are almond shaped and are the smallest of the paired major salivary glands. What is typically referred to as the sublingual gland actually comprises multiple glands—one major sublingual gland and multiple (8–30) minor individual sublingual glands. Each sublingual gland is located deep to the thin floor of mouth mucosa, lateral to the lingual frenum and genioglossus muscles, and is positioned in the sublingual fossa of the mandible, sitting on the mylohyoid muscle. The sublingual gland has no fascial capsule, unlike the other major salivary glands.

Parasympathetic fibers from the submandibular ganglion provide innervation to the sublingual gland and duct via the lingual nerve, similar to the submandibular gland. Sympathetic innervation, however, is derived from the cervical chain ganglia via branches from the facial artery.

Arterial and venous supply are via the submental branch of the facial artery and vein, and the sublingual branch of the lingual artery and vein.

Lymphatic drainage goes to the submandibular nodes and then the cervical chain of nodes.

The sublingual glands secrete mostly mucinous discharge and have a unique ductal system. About 8 to 20 smaller ducts of Rivinus exit the gland on the superior surface and empty into the anterior floor of mouth on the sublingual fold. Several of the more anterior ducts may converge to form a common Bartholin’s duct, which empties into Wharton’s duct.

Note

lymphatic drainage is via the submandibular nodes and secondarily the cervical chain of nodes.

18.4.5 Minor Salivary Glands

The minor salivary glands are composed of between 500 and 1,000 glands distributed throughout the upper aerodigestive tract. Each of these glands empties into the aerodigestive tract via its own simple duct. Although they can be found in the nasal cavity, larynx, and trachea, they are most prominent in the oral cavity and oropharynx. There are concentrations of glands in the buccal, labial, palatal, and lingual areas of the oral cavity. Minor salivary gland groupings in the superior tonsillar poles are known as Weber’s glands, and those at the base of the tongue are von Ebner’s glands.

Vascular supply and lymphatic drainage of the minor salivary glands vary based on anatomical location of the glands. In the oral cavity, postganglionic parasympathetic innervation is most commonly supplied via the lingual nerve, consistent with the submandibular and sublingual glands. On the palate, postganglionic parasympathetic supply travels from the sphenopalatine ganglion via the palatine nerves.

18.5 Development

There are currently two accepted theories on the cellular origins of salivary gland neoplasms; the multicellular theory and the bicellular theory.15 The multicellular theory suggests that the origin of a neoplasm is derived from a distinctive cell type within the salivary gland structure. According to this theory, acinic cell tumors are thought to arise from acinar cells, whereas squamous and MECs are thought to arise from the excretory duct cells. An alternative theory, the bicellular theory, suggests that the basal cells of the intercalated duct cells and excretory duct cells act as reserve cells for more differentiated cells in the salivary gland unit. The basal cells give rise to the columnar and squamous cells of the excretory duct and from there it follows that the excretory duct reserve cells give rise to squamous cell carcinoma (SCC) and MEC. The intercalated duct reserve cells give rise to the acinic cell and mixed tumor type carcinomas. The intercalated reserve duct cells are believed to be less aggressive than those tumors arising from the excretory reserve duct cells.

18.6 Classification and Staging of Salivary Gland Cancer

18.6.1 Evolving Classification System

Salivary gland tumors are classified as benign and malignant epithelial neoplasms, benign and malignant mesenchymal neoplasms, hematolymphoid tumors, and secondary tumors described in the literature. Salivary gland tumors may also be classified as low grade or high grade (Table 18.2). The most recent World Health Organization (WHO) histological classification of head and neck tumors was just over a decade ago in 2005.16 There have been many advances in histological and molecular methods of characterizing these cancers over the past decade, and several new entities described in the literature. Salivary gland tumors may also be classified as low grade or high grade (Table 18.3). This has been shown to have significant pragmatic information.

The North American Society for Head and Neck Pathology and the European Working Group for Head and Neck Pathology have developed “wish lists” of changes they hope to see in the next WHO classification of head and neck tumors. These have included dropping clear cell carcinoma NOS and changing these to hyalinizing clear cell carcinomas; changing cystadenocarcinoma to cystadenocarcinoma NOS, changing low-grade cribriform cystadenocarcinoma to low-grade salivary duct carcinoma, changing salivary duct carcinoma to high-grade salivary duct carcinoma, and adding sinonasal renal cell–like adenocarcinoma.17 Other requested additions to the next WHO salivary gland tumor classification list include sclerosing polycystic...
adenosis, mammary analogue secretory carcinoma, cribriform adenocarcinoma of the tongue and other minor salivary glands, and the mucinous variant of myoepithelioma.17,18,19

### 18.6.2 Stage

Staging of salivary gland tumors was last revised in 2002 by the American Joint Committee on Cancer (AJCC). Changes at that time included adding any tumor greater than 4 cm to be considered T3 (in addition to tumors having extraparenchymal extension) and dividing T4 lesions into T4a (resectable with grossly clear margins) and T4b (extension to areas that preclude resection with clear margins), leading to the division of stage IV into stages IVA, IVB, and IVC (▶ Table 18.4).

As in other sites, the TNM staging system qualifies the tumor, the node, and metastatic disease. The T stage is primarily based on the size of the tumor and whether extraparenchymal extension (defined as clinical, or macroscopic, evidence of invasion of soft tissues) is present, such as invasion of the extrinsic tongue muscles in sublingual and submandibular gland cancer, or invasion of the facial nerve in parotid gland cancers. The nodal and metastatic staging systems are the same for all tumors based in the aerodigestive tract. Diagnostic imaging studies may be used in staging but are not mandated unless lymph node metastases are suspected. The AJCC stage groupings follow the standard formula (▶ Table 18.5).

The minor salivary glands are staged according to their anatomical site of origin along the upper aerodigestive tract (i.e., oral cavity, pharynx, and sinuses). For example, a minor salivary gland tumor originating in the oral cavity will be staged according to the oral cavity TNM system. This can result in difficulties with classification of primary sublingual salivary gland cancers, as they can be clinically difficult to distinguish between primary minor salivary gland tumors of the floor of mouth. For
example, a 3-cm floor of mouth salivary gland tumor invading into adjacent extrinsic tongue muscles would be classified as a T3 tumor of the sublingual gland (stage III), versus a T4a tumor of a floor of mouth minor salivary gland (stage IVA).

**18.6.3 Grade**

The aggressiveness of a salivary cancer is often represented by the grade of the tumor. For example, MECs can be categorized into high-, medium-, or low-grade disease. High-grade MECs show a rapid and aggressive clinical course with early cervical metastasis and a propensity for local recurrence and distant disease. Conversely, low-grade MECs typically demonstrate a protracted, indolent course. Not surprisingly, management decisions are often made more on histological grade than cell type (Table 18.5).

**Note**

The nodal and metastatic staging systems for salivary gland carcinoma are the same for all tumors based in the aerodigestive tract.

**Table 18.5 Stage grouping**

<table>
<thead>
<tr>
<th>Stage grouping</th>
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<th>Stage II</th>
<th>Stage III</th>
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<tr>
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<td>T1 N1 M0</td>
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**18.6.4 Carcinoma of the Salivary Glands**

The most important predictors of distant metastasis were pathologic T and N stages, gender, perineural invasion, histological type, and clinical skin involvement (Table 18.5).

**Note**

Adenoid cystic carcinomas have a characteristic clinical course with a tendency for perineural invasion, local recurrence, and pulmonary metastasis.

Despite this generalized information, clinicians must realize that given the complexities of salivary gland histology, the grading systems continue to change, and different pathologists may disagree on the grade despite using the same criteria. This becomes important when deciphering comparisons between different studies done over varying time periods.

**18.7 Prognostic Factors for Salivary Gland Cancer**

Interestingly, the prognosis for early-stage salivary gland cancer has improved from 83 to 89% between 1983 and 1997. The exact reason for this is unknown. If it is due to better imaging, better access to health care, or different treatment modalities is unknown.

A retrospective study out of the Netherlands looking at nearly 600 patients with more than 10-year follow-up identified multiple independent prognostic indicators for locoregional and distant disease control as well as overall survival. Clinical T stage, positive margins, and bony invasion were all shown to be predictive of local recurrence. Complete facial nerve paralysis, pathologic nodal stage, and positive margins were independent predictors of regional failure. The most important predictors of distant metastasis were pathologic T and N stage. Sex, perineural invasion, histological type, and clinical skin involvement have been shown to be predictive of distant metastases.

Important independent factors that were associated with survival included positive margins, the number of positive neck nodes, extracapsular spread, perineural invasion, and vascular invasion.

**Note**

The most important predictors of distant metastasis were pathologic T and N stages, gender, perineural invasion, histological type, and clinical skin involvement.

**18.7.1 Surgery**

Patients who undergo surgery alone are nearly 10 times more likely to develop local recurrence, and two times more likely to develop regional recurrence compared to those who undergo surgery plus adjuvant radiotherapy in a high-risk population (T3 and T4 tumors, positive margins, bony invasion, and high-grade tumor).
Patients who undergo surgery alone are nearly 10 times more likely to develop local recurrence, and two times more likely to develop regional recurrence compared to those who undergo surgery plus adjuvant radiotherapy.

18.7.2 Stage
The stage at presentation of a patient with a salivary gland malignancy is the most well-studied prognostic factor.22,23 With regard to ACC, survival at 10-year posttreatment is highly correlated with stage, with 75, 43, and 15% of patients with stages I, II, and III or IV surviving, respectively.22

18.7.3 Surgical Margins
The adequacy of surgical resection has been found in numerous studies to be highly predictive of ultimate survival.24 The effect is so large that in one study of patients with ACC, those with negative surgical margins had a disease-free survival of 84% contrasted with a rate of only 17% in those with residual tumor at the margin of resection.25 There is evidence that the use of postoperative radiation in patients with positive margins can effect a substantial improvement in survival and should be considered in these patients.26

The adequacy of surgical resection has been found in numerous studies to be highly predictive of ultimate survival.

18.7.4 Grade/Histology
With numerous different histological types of salivary gland malignancies, much work has been done to determine whether histological type correlates with prognosis. Most authors divide salivary gland cancers into high- or low-grade histology.

Although often considered a high-grade cancer, ACC is unusual in that it often exhibits slow, relentless growth and with late recurrences both locally and distantly.

In MEC, high-grade histology has been found by several authors to predict increased incidence of local and regional recurrences as well as decreased survival.27,28

18.7.5 Facial Nerve Paralysis
Preoperative facial nerve paralysis has been found by multiple authors to be an adverse prognostic factor in patients with salivary gland carcinoma. It is difficult to isolate the effect of stage in these patients because patients with facial palsy tend to have larger tumors. Nevertheless, several studies29,30 have confirmed the relatively grim prognosis of patients who develop facial paralysis during the course of their disease progression (Fig. 18.4).

The propensity for high-grade malignancies to metastasize to the neck is unusual, so it is rare that a salivary gland tumor presents as a neck mass distinct from the primary glandular tumor.

18.7.6 Cervical Metastasis
As with other head and neck malignancies, the presence of cervical lymph node metastasis in patients with salivary gland cancer has been found to adversely impact survival.

18.8 Clinical Presentation
18.8.1 History
Salivary gland malignancies demonstrate great variability with respect to natural history. They commonly present as a firm, painless mass within the affected gland. The propensity for high-grade malignancies to metastasize to the neck is unusual, so it is rare that a salivary gland tumor presents as a neck mass distinct from the primary glandular tumor.

Although both benign and malignant tumors may present as a firm mass, malignancies may be fixed to the underlying soft tissue or, in advanced cases, present with a palsy of the named nerve(s) in closest proximity to the affected gland.
Carcinoma of the Salivary Glands

Pain is considered an ominous sign and is usually associated with perineural invasion, which has been associated with ACC. Other possible symptoms of perineural spread are dependent on the nerve involved: numbness/paresthesia/pain of the lower lip, teeth, or tongue (V3), facial twitching or partial facial paralysis (VII), dysphagia (IX), voice changes due to vocal fold paresis (X), or dysarthria due to partial tongue paresis (XII).

18.8.2 Physical Examination

Clinical presentation is dictated by the stage and the gland afflicted with the tumor. Physical examination should include a complete head and neck examination including determination of the character, size, and location of the primary tumor, palpation for cervical lymphadenopathy, oral and oropharyngeal examination, fiberoptic nasopharyngoscopy, and a cranial nerve examination. Facial nerve palsies have been independently correlated with regional recurrence, and skin invasion has been independently predictive of distant metastases by 10 years after initial surgical therapy.

18.8.3 Parotid Gland

The tail of the gland is the most common site of presentation for the typical painless mass, and depending on the physical habitus of the patient, tumors may achieve an advanced stage before being detected. As the tumor increases in size, it rarely affects facial nerve function. When facial nerve function is affected, it is usually associated with a high-grade malignancy such as SCCs, high-grade MECS, and/or adenoid cystic cancer. Less aggressive salivary tumors may grow extensively before causing a facial nerve palsy. Parapharyngeal parotid tumors can present as an oropharyngeal submucosal mass. Mass effect can result in dysphagia, and if the tumor extends to the pterygoid musculature trismus may also be a presenting finding.

18.8.4 Submandibular Gland

Tumors of the submandibular gland typically present as a painless mass in the submandibular triangle. The structures arising in this area such as the lingual and hypoglossal nerves are uncommonly affected unless there is extracapsular spread. More advanced submandibular gland cancer can invade into the mandible causing pathologic fracture and affecting the inferior alveolar nerve. Invasion into the medial pterygoid can result in trismus with a hard stop.

18.8.5 Sublingual Gland

Tumors of the sublingual glands typically present as a painless mass in the anterior floor of mouth. Seldom is there ulceration; however, advanced tumors may present as an ulcerative lesion. More advanced cases can present with invasion of the lingual or hypoglossal nerves, similar to submandibular gland cancer.

18.8.6 Minor Salivary Glands

Minor salivary gland cancer also typically presents as a painless mass, with variable signs and symptoms depending on the location of the glands involved. Lower lip masses are often asymptomatic aside from soreness associated with biting the swollen lip. They may coincide with lower lip paresthesia if the mental nerve has been invaded. Minor salivary gland cancer of the hard palate can extend into the pterygoid musculature resulting in trismus, or it may grow up and around the maxillary dentition resulting in dental complaints.

18.9 Diagnosis and Workup

18.9.1 Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) represents an essential component in the workup of an unknown neck mass. The role of FNAB for salivary gland tumors, however, is less clearly defined, and has been a source of controversy. This apparent discrepancy stems from the inherent difficulty of confirming the histological diagnosis of a salivary malignancy. The majority of unknown cervical metastases are easily identified as SCC; however, the variety of salivary gland histology often requires special expertise for interpretation. Complicating this is that low-grade salivary cancers are easily confused with benign neoplasms even on permanent pathologic analysis. Unlike an unknown neck mass where the histological diagnosis profoundly impacts therapeutic strategy, the results of FNAB will seldom change the initial surgical treatment of a salivary gland tumor. For parotid tumors, the minimal uniformly accepted resection of a suspicious lesion is a superficial parotidectomy. Similarly, excisional biopsy of the submandibular gland is the core treatment of any submandibular neoplasm. Despite these logistic limitations, many clinicians rely on FNAB in the preoperative workup of patients with suspected salivary cancer.

Fine-needle aspiration biopsy represents an essential component in the workup of an unknown neck mass; however, there is an inherent difficulty of confirming the histological diagnosis of a salivary malignancy.

The safety and accuracy of FNAB for salivary gland malignancies is well established. Early concerns of tumor seeding from the needle track have been dispelled. In high-volume centers with qualified personnel, FNAB is a simple, safe, and informative test. Multiple large studies from across the globe have confirmed FNAB to be exceptionally accurate and reliable when performed by an experienced cytopathologist. The distinction between benign and malignant tumors is possible in most cases. The sensitivity of FNAB for salivary gland tumors has been reported as high as 85 to 95% with a specificity approaching 100%. FNAB is far less accurate when interpreted by less-experienced practitioners. The results of FNAB should always be interpreted with caution. FNAB results are typically reported as benign, malignant, indeterminate, or inadequate. A “negative” FNAB has little meaning as this usually represents either an inadequate or indeterminate specimen. Inadequate sampling of the lesion is the most common diagnostic error. If recognized immediately, inadequate FNAB results should prompt a second biopsy; second biopsy has shown to be beneficial even in the case of indeterminate results.
Even when an FNAB is indeterminate, the description of histological findings often offers clues that may help direct further workup. Therefore, it is incumbent upon the clinician to carefully analyze every detail of the written pathology report. For example, monomorphic lymphocytes noted on FNAB may be suggestive of salivary gland lymphoma prompting further investigation. Such indeterminate FNAB results, albeit helpful, are unlikely to be resolved by repeated FNAB. A more invasive approach is frequently required to pinpoint a diagnosis in these cases.

Not all patients with salivary tumors require FNAB. FNAB is best employed when the results will impact treatment or patient counseling. The results of FNAB may change the planned extent of surgical resection. Specifically, patients with confirmed malignancy on FNAB would be considered for selective cervical lymph node dissection based on the stage and grade of disease. Special attention may also be given to the preoperative planning of possible facial nerve resection and reconstruction for those patients in whom an FNAB confirms parotid malignancy. Although this is controversial, many surgeons will not resect the facial nerve if it functions. They feel normal facial nerve function outweighs a positive margin. FNAB is important for differentiating tumors of salivary origin from those that are systemic or metastatic. For example, the diagnosis of lymphoma may be suggested by FNAB and, if confirmed with more tissue, could spare the patient extensive surgery. FNAB can also be helpful in counseling patients who are poor surgical candidates. An unsuitable surgical patient with the diagnosis of benign disease on FNAB can be observed. Thus, FNAB may be more important for defining those patients who will not need surgery rather than in helping to plan surgery for known operative cases.

**Note**

Even when an FNAB is indeterminate, the description of histological findings often offers clues that may help direct further workup.

### 18.9.2 Imaging

Imaging is recommended for all salivary gland lesions because it allows for defining the size and extent of the tumor in addition to its relationship to critical structures such as the facial nerve. It is particularly helpful for minor salivary gland cancers where assessment of bone invasion or submucosal spread is critical for treatment planning. Specific indications for anatomical imaging include clinical uncertainty of tumor extent, evaluation of deep lobe or extraglandular involvement, identification of facial nerve invasion, and identification of potential cervical lymph node metastasis. Anatomical imaging is also useful for evaluating recurrent disease where differentiation between tumor and scar can be difficult. Functional imaging has limited utility for the evaluation of salivary gland malignancies except to identify rare distant metastasis.

Computed tomography (CT) and magnetic resonance imaging (MRI) can be useful in evaluating salivary gland tumors. The most recent National Comprehensive Cancer Network (NCCN) treatment guidelines added with contrast to the CT or MRI imaging guidelines if clinically indicated. Although each modality has inherent advantages and disadvantages, both techniques can provide valuable information. CT is capable of ruling out a salivary duct stone, which is poorly visualized using MRI. CT is also better suited for evaluating erosion of the mastoid or mandible. In contrast, bone marrow involvement is better demonstrated with MRI; however, CT is less expensive than MRI and is more widely available. Contrast-enhanced CT provides the advantage of being able to better define areas of necrosis in highly vascularized tumors but is more subject to dental artifact (▶ Fig. 18.5). By comparison, MRI provides greater soft tissue detail. MRI allows for visualization of pathology in three orthogonal planes: axial, coronal, and sagittal. MRI provides better delineation of tumor architecture compared with conventional CT. MRI is particularly well suited for differentiating deep-lobe parotid tumors, classically located in the prestyloid compartment, from other lesions of the parapharyngeal space.
Perineural spread of tumor is also best visualized using MRI. For these reasons, MRI is more widely accepted as the imaging modality of choice for the evaluation of salivary gland malignancies.35 The benefit of preoperative imaging for salivary gland cancer is roughly proportional to the stage of the disease. Early-stage salivary gland cancer can be managed without imaging if the clinical examination is reliable. For advanced-stage malignancies, both CT and MRI may be required to fully evaluate the extent of tumor involvement and often provide complimentary information. For example, CT may be used to assess bone destruction and to survey potential cervical metastasis. MRI can be used then to further define tumor composition and position relative to nearby soft tissue structures, as well as to assess for perineural invasion. MRI can be essential for evaluating potential intracranial extension of disease. Additional special studies may be useful for evaluating aggressive, advanced-stage salivary malignancies. Angiography and magnetic resonance angiography (MRA) can be used to assess carotid invasion. Functional imaging such as positron emission tomography (PET) can be used to screen for distant metastasis.

Note
CT may be used to assess bone destruction and to survey potential cervical metastasis while MRI can be used then to further define tumor composition and position relative to nearby soft tissue structures, as well as to assess for perineural invasion.

The utility of [18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for the routine evaluation of salivary gland malignancies has yet to be established. Both benign and malignant histology are well visualized using FDG-PET. The sensitivity of FDG-PET in the detection of salivary gland cancer is high but carries a false-positive rate of nearly 30%. Warthin’s tumors and oncocytesomas are most likely to be confused with salivary malignancy using FDG-PET, presumably because of the high mitochondrial content of these lesions (▶ Fig. 18.7). Although the standard uptake value (SUV) is generally higher for malignant salivary lesions compared with benign neoplasms, there is considerable overlap. Given current technology, functional imaging techniques cannot reliably differentiate benign from malignant salivary pathology. FDG-PET does not provide anatomical information and therefore cannot be used in place of CT or MRI in the evaluation of a salivary gland malignancy. FDG-PET can be used to screen for distant metastasis; however, the incidence of distant metastasis is low, limiting the clinical utility of FDG-PET in the routine workup of salivary cancers.36

Summary: Imaging and Fine-Needle Biopsy
Historically, the greatest controversy surrounding the management of salivary gland cancers has revolved around the utility of preoperative imaging and FNAB. As discussed previously, neither anatomical imaging nor FNAB is required for every salivary malignancy. The clinical utility of FNAB for salivary cancer depends largely on the interest and expertise of the cytopathologist. Similarly, the utility of anatomical imaging depends on accurate interpretation of the study. No investigation can supplant clinical acumen. Even so, many clinicians utilize one or more of these investigations routinely. The decision to use preoperative imaging or FNAB, then, tends to rest more on personal philosophy and logistics rather than on science. Experienced head and neck surgeons selectively employ anatomical imaging and FNAB tailored to the tumor location and clinical presentation of each patient. Patients with advanced-stage tumors will frequently benefit from both investigations. Conversely, patients with small, well-circumscribed, low-grade lesions can be managed based on clinical examination alone.
18.10 Treatment

In most cases, the treatment of salivary gland tumors is primarily surgical with the use of adjuvant postoperative radiation therapy based on the presence of adverse pathologic factors including high-grade histopathology; large tumors; extracapsular extension; extension into skin, temporal bone, skull base, or mandible; facial nerve involvement; or cervical lymphatic metastasis. Radiation therapy has been used in cases where the tumor is unresectable because of either technical factors or patient comorbidities. Surgical resection should be focused on complete resection with adequate margins of normal tissues, and undue morbidity should be avoided. Of particular concern is facial nerve function. When the facial nerve is not invaded or encased by tumor, every attempt should be made to preserve the nerve. If, however, the tumor cannot be completely removed without resecting all or a portion of the nerve, then the nerve should be sacrificed. On occasion, salivary gland tumors will involve the skin of the face, mandible, or temporal bone. All of these structures can be resected en bloc with the tumor and represent more of a reconstructive challenge than one of resection. If for technical reasons or because of patient’s wish a tumor cannot be completely resected, then consideration should be given to alternative, nonoperative management as there is little evidence that partial resection benefits the patient in terms of survival and probably just results in added morbidity to the treatment.

**Note**

Because surgical margins are such an important prognostic factor, if the tumor cannot be completely removed without resecting all or a portion of the nerve, then the nerve should be sacrificed.

18.10.1 Parotid Gland

Tumors of the parotid gland that are small and located within the superficial lobe of the parotid gland can often be managed by superficial parotidectomy. Deep-lobe tumors or those that involve both the superficial and deep lobes usually require total parotidectomy (Fig. 18.8). The term total parotidectomy is a misnomer as it is technically difficult to remove all of the parotid gland due to its extensions around the external auditory canal and deep to the mandible. When extension outside of the parotid fascia occurs, surgical resection of the involved structures should be performed in an en bloc fashion (Fig. 18.9). This may require resection of the skin overlying the parotid, the mandible, or portions of the temporal bone. When such structures require resection, various reconstructive options exist that are discussed in Chapter 19.

Preservation of the facial nerve should be considered unless there is direct invasion. When the surgeon encounters facial nerve invasion or encasement by a malignant neoplasm, the involved portion of the nerve should be resected. The nerve can be repaired primarily if a neurorrhaphy can be accomplished without tension. This is uncommon, and in most cases a nerve graft is required. Defects less than 4 cm can often be repaired with a graft obtained from the great auricular nerve if the nerve is available. When the defect is longer than 4 cm or the great auricular nerve is unavailable, then the sural nerve is a good reconstructive option.

When the tumor approaches the stylomastoid foramen or if perineural extension extends into the temporal bone, a mastoidectomy and removal of the mastoid tip can provide enhanced exposure. Mastoidectomy and intratemporal identification of the facial nerve can be particularly helpful in the case of reoperative parotid surgery as it allows identification of the nerve in a previously unoperated field.
Carcinoma of the Salivary Glands

18.10.2 Submandibular Gland

Neoplasms of the submandibular glands are less common than tumors of the parotid gland. Management of submandibular gland tumors in general carries less risk of damage to the facial nerve (except for its marginal mandibular branch), but there are other nerves located within proximity to the submandibular gland, specifically the lingual and hypoglossal nerves.

Surgery for tumors of the submandibular gland should be performed differently than surgery for benign inflammatory conditions of the gland. Whereas the latter can often be managed with a subcapsular enucleation of the gland, malignant tumors should be removed with a more comprehensive procedure. When the exact nature of the tumor is unclear, the procedure should be directed to adequately resect the tumor as if it was malignant. If the condition ultimately is found to represent an inflammatory condition, there are little adverse consequences to the patient.

18.10.3 Minor Salivary Glands

Minor salivary glands typically present as floor of mouth or oral cavity tumors. They may arise in the soft or hard palate and present as a submucosal mass. Treatment is the same as for a mucosal carcinoma with wide local excision and negative margins. It is oftentimes hard to preserve the overlying mucosa so a mucosal defect is created. It is not necessary to remove as much mucosa with as large a margin as when resecting a mucosal tumor.

Management of the Neck

Management of the neck can be divided into two clinical scenarios: patients with clinically evident lymph node metastasis and those with a clinically N0 neck. In patients with clinical evidence of metastasis, a neck dissection is an essential aspect of the management. In general, this should consist of a comprehensive neck dissection. Decisions regarding preservation of nonlymphatic structures (modified and selective neck dissections) should be based on clinical findings during the time of operation. There are little data regarding the use of superselective neck dissection in the setting of neck disease, and therefore its use cannot be commented on.

In patients with a clinically N0 neck, the risk of occult cervical metastasis depends on multiple factors. Tumors larger than 4 cm, those with high-grade histology, extension beyond the capsule of the parotid gland, and those with preoperative facial nerve paralysis have a high rate of occult cervical lymph node metastasis. Therefore, an elective cervical lymphadenectomy is indicated. There is no consensus regarding the type of neck dissection to perform. Certainly, it seems acceptable to preserve the spinal accessory nerve in these patients. Also, the use of selective neck dissection in this setting as a staging operation seems a reasonable consideration.

As more local composite tissue is resected, the need for composite tissue reconstruction increases. This usually means free tissue transfers, exploration for vessels is best done in conjunction with a staging neck dissection.

18.11 Nonsurgical Treatment

Surgery is the primary therapeutic modality for malignant tumors of salivary origin that are local or locally advanced and amenable to resection with clear margins without undue morbidity related to adjacent anatomical structures. When high-risk features are noted on pathologic examination, surgery should be followed by adjuvant radiation in an effort to prevent locoregional recurrence.

When the tumor is unresectable due to either technical factors or patient comorbidities, primary radiation therapy may be considered. Patients with distant metastatic disease, or those with locoregional disease not amenable to surgery +/- radiotherapy, will continue to progress and worsen if not treated. In these cases, chemotherapy, targeted therapies, and hormonal treatments are alternative options.

Nonsurgical management is currently restricted to the management of inoperable tumors or to palliative management.

18.11.1 Radiation Therapy

Postoperative adjuvant radiation therapy augments locoregional control of appropriately selected patients with aggressive salivary cancers. There is additional evidence to suggest that it may improve disease-specific survival as well for this cohort. Postoperative radiotherapy is typically advised for advanced-stage and or high-grade disease where the risk of
locoregional failure is high. Additional indications for adjuvant postoperative radiation therapy include positive surgical margins, recurrent disease, and other unfavorable pathologic characteristics. It may be that radiation therapy changes the pattern of recurrence. Most failures after radiation therapy occur as distant metastasis.

Postoperative radiotherapy is typically advised for advanced-stage and/or high-grade disease where the risk of locoregional failure is high.

The role of radiotherapy for palliation of inoperable or recurrent salivary malignancy is also increasingly recognized. Responses have been reported in a sizable proportion of patients. Long-term local control with metastasis-free survival has been reported in more than 50% of patients. Fast neutron radiation therapy may offer a biological advantage for treating inoperable salivary gland cancer, particularly ACC. A randomized study comparing neutron therapy versus conventional photon or electron radiotherapy for unresectable salivary malignancy demonstrated improved locoregional control for the neutron therapy cohort. Increased morbidity was noted for patients receiving neutron beam radiotherapy. For this reason, and because few facilities are capable of delivering neutron therapy, conventional photon beam radiotherapy is still recommended for the majority of patients with unresectable salivary gland cancer.

18.11.2 Systemic Therapy

The aggressive nature and tendency for high-grade salivary cancer to metastasize to a distant location highlight the need for systemic therapy in selected patients. However, given the relative rarity of salivary gland cancers, and the widely varying histological types, gathering large enough sample sizes for evidence of a therapeutic effect is challenging. The indolent natural history of disease progression limits conclusions that can be drawn with respect to disease stabilization after a particular systemic therapy unless the study requires disease progression prior to enrollment. Thus, the goals of systemic therapy should be for disease stabilization of previously progressive disease, and/or symptom improvement for disease-related symptoms.

Chemotherapy

Unfortunately, the results of chemotherapy for treating salivary gland malignancy have been disappointing, as no survival benefit has been shown.

A recent examination of the National Cancer Database (NCDB) data identified over 2,200 patients from 1998 to 2011 who had resection of grade II–III major salivary gland carcinomas with at least one high-risk feature (T3–T4, node positive, or margin positive). After primary surgical therapy, all patients underwent either adjuvant radiotherapy or adjuvant chemoradiation. All survival outcomes were worse or equivalent when adding chemotherapy (both single and double agent) to adjuvant radiotherapy. Recent evaluation of the SEER database of patients from 1992 to 2009 who underwent primary surgical therapy and adjuvant treatment drew the same conclusions, showing median overall survival of 41 months with adjuvant radiotherapy, compared to 24 months with chemoradiotherapy.

Given the lack of evidence of efficacy observed to date, differing dosages and regimens, and small sample sizes in the available studies, adjuvant chemotherapy is not currently advised outside of a clinical trial.

Even palliative chemotherapy has had limited response rates, ranging from 0 to 40%, even when including partial responses. Radiologic response to systemic chemotherapy has not been shown to improve disease-free or overall survival rates. Given these findings, chemotherapy should be reserved for palliation only in patients with rapidly progressive disease, and/or significant disease-related symptoms. The real objective of palliative chemotherapy is improvement in quality of life, which results from a decrease in disease-related symptoms for the patient that outweighs the side effects of therapy. Response rates for ACC have been quite different to those in MEC.

For severe symptoms related to disease in patients, who cannot have surgery, one could consider initial treatment with a combination of platinum and anthracycline to maximize the possibility of a response, or single-agent therapy.

Combined Chemoradiation

Single-Agent Chemotherapy

Chemotherapeutic drugs used as monotherapies have had very limited responses, and when patients do respond it tends to be for a short period of time.

Agents with the most activity in salivary gland cancer are cisplatin, doxorubicin, and fluorouracil (5-FU). Stabilization of tumor growth with limited regression has been reported using a variety of agents. Overall the literature is of small case series with limited benefit.

Combined-Agent Chemotherapy

Overall, higher response rates have been reported, but with more toxicity, and no clear benefits or clinically meaningful outcomes when compared to their significant toxicity. In general, the survival benefit is minimal and the morbidity is significant. While response rates of up to 35% are reported, they may not provide a meaningful improvement in quality of life. The use of multiple regimes has been limited to patients who are very symptomatic, thus it is hard to compare the studies published to date.

Molecular Targeted Therapy

The results of targeted therapy have generally been disappointing. There have been few responses in phase II trials, while high initial stabilization rates and some long-term stabilizations have been reported, many trials started therapy before progression of disease, and given the often indolent nature of the disease, it is hard to measure the history of the disease or a drug’s effect. Studies showing a short duration of disease stabilization are not reliable because of the indolent natural history of salivary gland cancers.
18.12 Reconstruction

Reconstruction of defects after ablative surgery for salivary gland tumors primarily deals with parotid gland defects. Minor salivary gland tumors when resected require some form of composite resection, which is not much different from a composite resection of the overlying oral cavity mucosa and surrounding structures. Their reconstructive paradigms follow the reconstruction for that particular anatomical subsite. The same can be said for submandibular gland tumors, which usually only require reconstructive consideration when they involve the mandible or extend up into the tongue.

Defects of the parotid gland have undergone an evolution in terms of reconstructive aspects. Management of parotid gland tumors depends significantly on whether the facial nerve is involved or not. If the facial nerve is involved, then sacrifice is usually mandated. Reconstruction of patients who have had their facial nerve resected is complex. Needless to say, management of the eye is of paramount importance at the initial setting. Gold weight placement and lateral tarsal strip have been found to be quite useful in these instances. The facial nerve usually can be reconstructed at the initial setting using a nerve graft. There are many sites available for a nerve graft. The sural nerve is the most common, but the medial antebrachial as well as greater auricular have been used with equal success. In the setting of malignancy involving the facial nerve, postoperative radiotherapy is often administered. There has been some concern that this may inhibit or affect the ultimate outcome of the facial nerve, but it has been well documented that preoperative or postoperative radiotherapy has no impact on ultimate facial nerve function.46

Another issue that has arisen is the effect of perineural invasion at the margin of the resection. Several carcinomas are notorious for traveling along the nerve and leaving perineural positive margins either peripherally or centrally. A recent study has documented that this has no effect on ultimate outcome and should not influence whether to reconstruct the facial nerve. Most patients who have parotid malignancies, even if they do involve the facial nerve, have good 2- to 5-year survival, and reconstruction should be undertaken in all of these patients.47

Management of the lateral commissure is more problematic. Loss of the facial nerve will result in a drooping of the lateral commissure and relaxation of the elevators at the corner of the mouth. This has a significant effect not only on cosmesis but also on function (from a drooling and deglutition perspective). Patients are often quite debilitated by this. Immediate reconstruction provides immediate relief of the symptomatology.

The other area of major concern in total parotidectomy or in patients who have also undergone neck dissection is the cosmetic defect. The skin is the only outer envelope that is retained, and the masseter muscle as well as mandible is the next layer. This leaves quite an indentation on the lateral aspect of the facial skeleton and should be reconstructed. Free fat grafts have been used in the past, but their survival and retention of bulk is quite variable. We would suggest that a soft tissue reconstruction should be done on all of these patients. Free tissue transfer using an anterolateral thigh flap or a deepithelialized radial forearm flap will provide enough soft tissue to fill in the soft tissue defect. The trade-off is a cosmetic defect on the volar aspect of the forearm or a long scar on the leg. The gain in a permanent predictable soft tissue augmentation in the cheek is considerable. Patients are usually pleased with their outcome and do not feel they are cosmetically deformed. True quality of life measures are absent.48

18.13 Posttreatment Surveillance

Surveillance recommendations after initial definitive surgical, systemic, or radiation therapy for salivary gland cancers are the same as for other head and neck cancers. Head and neck examinations should be completed every 1 to 3 months during year 1, every 2 to 6 months during year 2, and every 4 to 6 months during years 2 to 5. While these numbers are recommended, there is little evidence to suggest that routine surveillance impacts detection of local regional recurrence or impacts survival. While there is an abundance of literature for SCC of the mucosal surfaces of the head and neck that supports routine surveillance, little exists for salivary gland disease. Perhaps the most beneficial aspect of surveillance is the development of the patient–doctor relationship and the psychological well-being of the patient.

Note

Surveillance after treatment should include a head and neck examination every 1 to 3 months during year 1, every 2 to 6 months during year 2, and every 4 to 6 months during years 2 to 5.

Posttreatment imaging for patients who received primary surgical therapy is controversial. An argument has been made that the site of salivary gland and tumors is buried and recurrence may not be detected with physical examination or patient symptomatology at an early enough stage to allow for intervention. Thus, imaging of some form is suggested. Arguing against this is the understanding that patients with high-grade tumors who are most likely to recur in the local regional area will most likely have undergone ancillary treatment and thus they will recur as metastatic disease. With little-known efficacious treatment modalities for the metastatic disease, detection may not be beneficial at this stage. In patients whom we wish to follow we would start with a CT or MRI of the primary tumor site and neck within 6 months of definitive therapy. Reimaging or not after this baseline is guided based on signs/symptoms, and accessibility of the primary tumor site to clinical examination. There are no specific guidelines for posttreatment FDG-PET/CT in these patients.

Patients with persistent or progressive disease 1 to 2 months after systemic or radiation therapy should have a CT and/or MRI with contrast of the primary site and neck, with or without FDG-PET/CT to evaluate for distant metastases. In initial responders, posttreatment imaging should be delayed until 2 to 4 months posttreatment for CT and/or MRI with contrast to evaluate the primary site and neck, or FDG-PET/CT to evaluate for distant metastases.
Chest imaging is recommended only in smokers and should be based on the NCCN guidelines for lung cancer screening of smokers; no specific guidelines on chest imaging for head and neck cancer patients exist.

Patients who have received radiation to key anatomical areas of the head and neck should receive follow-up as appropriate—dental evaluation for oral cavity radiation, speech and swallowing evaluation as needed for oropharyngeal and hypopharyngeal radiation, and thyroid-stimulating hormone (TSH) monitoring every 6 to 12 months after neck radiation. Ongoing surveillance and management or referral for depression, smoking, alcohol, nutrition, speech, and swallowing problems should take place as for any head and neck cancer patient.

18.14 Clinical Cases

18.14.1 Case 1

Management of long-standing parotid mass.

Presentation
An 83-year-old woman presented with a slow-growing mass in the left parotid region. The mass was approximately 5 cm in size and had been present for the past 20 years. When she originally consulted a physician 20 years ago, she was scheduled to have the mass removed but suffered a stroke and in the recovery phase, neglected to have the parotid mass followed.

Physical Examination
Physical examination revealed an immobile mass located in the tail of the parotid. Facial nerve function, cranial facial examination, and head and neck examination were negative. The patient was wheelchair bound, slightly aphasic, and had a history of cardiac myopathy with tenuous status due to her congestive heart failure.

Diagnosis and Workup
Computed tomography and MRI scans demonstrated a cystic-appearing mass with distinct borders. FNAB confirmed Warthin’s tumor.

Treatment of the Primary Tumor
The pathology and radiographic findings combined with a 20-year history of slow growth confirm that this is a benign lesion. Given this woman’s tenuous medical status and the lack of concern for cosmesis, a decision is made to continue to follow the tumor.

Over the next 2 to 3 years, the mass slowly increases in size to approximately 6 cm. No active intervention was undertaken, and the woman passed away one evening in her sleep.

Summary of Treatment
This case demonstrates how watchful waiting and observation is appropriate in a certain patient population with well-defined histopathology.

18.14.2 Case 2

Management of the subacute parotid mass.

Presentation
A 24-year-old man presented with a 1.5-cm nodule anterior to the tragus. This mass was first noticed approximately 2 to 3 months prior to presentation. It had slowly increased in size but was otherwise asymptomatic. The patient had no complaints concerning the ear, nose, and throat. He had no infectious etiology or exposure.

Physical Examination
His physical examination was unremarkable with the exception of a mobile 2.5-cm mass anterior and inferior to the tragus.

Diagnosis and Workup
In view of the gentleman’s recent exposure to a cat, an FNAB was performed. Pathologic features consistent with a pleomorphic adenoma were identified on cytology. A CT scan confirmed the presence of a superficial lobe parotid tumor with well-defined borders.

Treatment of the Primary Tumor
Through a standard parotidectomy incision, the lesion was removed after identification of the facial nerve. The mass was found to lie between the buccal and the ramus mandibularis branch of the facial nerve. These nerves were preserved, and a SCM flap was positioned into the defect to preserve cosmesis. Final pathology revealed a pleomorphic adenoma, and the patient healed well with no sequelae.

Summary of Treatment
This case demonstrates how a careful history is required to rule out etiologies other than benign neoplasms. Cat scratch fever, though a rare cause of a lymphadenopathy in the parotid gland, should always be considered. FNAB was performed for that reason in this case, and imaging was believed to not contribute to either the diagnosis or management, so was not done. Although a large number of surgeons do not reconstruct the parotid defect, given this gentleman’s young age and concern over cosmesis, a small myogenous rotational flap was used to obliterate the dead space and improve the postoperative cosmetic appearance.

18.14.3 Case 3

Management of a low-grade malignant parotid lesion.

Presentation
A 56-year-old man presented with a 3-month history of a facial mass located at the angle of the mandible. It was noticed while he was shaving and had not bothered him. He thinks that it may have increased in size over the past month or so but has not been associated with other symptoms.
### Carcinoma of the Salivary Glands

#### Physical Examination

Physical examination revealed a firm indistinct mass in the angle of the mandible. It was approximately 3 cm and mobile. Cranial facial examination demonstrated that the facial nerve and the head and neck examination were normal.

#### Diagnosis and Workup

An FNAB was performed and revealed a mixed population of cells suggestive of a malignancy; however, a definitive diagnosis could not be made. An MRI scan was performed because of the indistinctness of the mass, and it revealed a bilobed tumor that extended into the parapharyngeal space. The borders were indistinct suggesting a malignant etiology.

#### Treatment of the Primary Tumor

The patient was counseled and taken to the operating room. A standard parotidectomy was performed through a standard approach, and the facial nerve was identified. Intraoperative examination revealed a tumor that was deep to the ramus mandibularis nerve extended into the parapharyngeal space. Through a standard approach, the mass was resected, and pathology revealed a low-grade MEC. Because the tumor was “low-grade,” no adjuvant therapy was recommended.

#### Summary of Treatment

This case demonstrated how a mass that is indistinct in the parotid on examination requires radiographic investigation to determine the anatomical boundaries. FNA was essential in counseling the patient regarding possible facial nerve resection. The grading of MEC is based on the cystic component of the tumor, neural invasion, necrosis, mitoses, and anaplasia. In general, the more squamoid and less mucinous features associated with the histology, the more high grade the tumor. Whereas high-grade MEC is commonly treated with postoperative radiation therapy after surgery, low-grade tumors can be managed with surgery followed by close observation. Intermediate-grade cancers represent a controversial subgroup. The decision to observe or radiate is usually based on the margin status.

#### 18.14.4 Case 4

Management of a parotid lesion with facial nerve involvement.

#### Presentation

A 56-year-old man presented with a 3-month history of a gradually expanding mass in the right parotid region. His history was interesting in that approximately 7 years ago, he had a large SCC removed from his temple. Margins were negative at that time. The parotid mass had been slowly increasing in size, and he found that he was unable to elevate his brow as he used to do in the past. At the end of the day he would have trouble reading, as the brow “hanged” over the eye. He was otherwise well and asymptomatic.

#### Physical Examination

His physical examination confirmed that the upper branch of his facial nerve was not functioning well. There was a weakness of the closure apparatus of his eye. He was able to close the eye, but when the examiner attempted to open the eye, it was relatively easy to compare with the contralateral side. Furthermore, the eyebrow was seen to hang down over the eye producing a hooding effect. He could lift the eyebrow but movement was sluggish. The rest of his facial nerve and craniofacial examination was normal. He had a 4-cm, firm, hard mass in the right parotid gland that appeared fixed to the underlying tissues. There was no other lymphadenopathy present. A CT scan and MRI scan revealed a single 4-cm inhomogeneous mass in the right parotid gland. It appeared fixed to the inferior portion of the zygomatic process. There was no other lymphadenopathy present.

#### Diagnosis and Workup

An FNAB confirmed SCC. The patient was presented at tumor board, and the parotid tumor was believed to be a metastatic SCC from a primary on his temple. It is believed that combined modality treatment with surgery followed by postoperative radiotherapy would be his best management.

#### Treatment of the Primary Tumor

He proceeded to the operating room where a total parotidectomy and level II to IV neck dissection were performed. In conjunction with this, the facial nerve was sacrificed.

At the time of his initial ablative procedure, a deep epithelialized radial forearm fascial cutaneous free flap was placed in the wound bed. This allowed for rehabilitation and reconstruction of the soft tissue defect. A nerve graft of the medial antebrachial nerve was harvested and connected from the facial nerve stump to the peripheral branches. At the same time, the upper eye was rehabilitated with the placement of a 1.2-mg gold weight, and a lateral canthal strip procedure was performed. A stitch to expand and stabilize the nasal valve was placed, and an acellular dural matrix sling was used to suspend the lower lip.

#### Summary of Treatment

This case demonstrates that large ablative procedures involving the facial nerve and the soft tissues of the face are best rehabilitated by reconstructing the facial nerve with a graft for long-term rehabilitation and then by various facial plastic procedures to rehabilitate the eye, both its upper and lower lid components and the midface and lower face. The contour secondary to the soft tissue loss is reconstructed with a free tissue flap.

#### References

19.1 Introduction
Complex parotidectomy defects arise from the surgical management of primary parotid malignancies, metastases to the parotid gland, temporal bone malignancies, or deeply invasive cutaneous malignancies. Surgical resection of these tumors may require resection of the overlying facial skin, auricle, parotid, facial nerve, mandible, and temporal bone, resulting in significant change of facial symmetry and appearance. The reconstructive surgeon should be prepared to perform soft tissue and bony reconstruction and facial nerve rehabilitation. In this chapter, we present our principles and goals of parotid reconstruction as well as the most relevant reconstructive options for parotid reconstruction and facial nerve rehabilitation.

19.2 Relevant Anatomy
The parotid gland is divided into superficial and deep lobes, separated by the facial nerve and the retromandibular vein. The facial nerve is superficial to the retromandibular vein. The facial nerve has five major extracranial branches: frontal, zygomatic, buccal, marginal mandibular, and cervical branches. The frontal branch runs along a line from a point 5 mm below the tragus to a point 1.0 to 1.5 cm above the lateral margin of the eyebrow. The frontal branch innervates the frontalis, superior aspect of orbicularis oculi, and corrugator supercilii muscles. The zygomatic branch innervates the zygomaticus major and minor, levator labii superioris alaeque nasi, depressor septi, and dilator naris muscles. The buccal branch innervates the buccinator and the superior aspect of the orbicularis oris. The buccal branch is often intimately associated with the parotid duct. The marginal mandibular branch of the facial nerve runs superficial and perpendicular to the facial vessels in the facial notch of the mandible. This branch innervates the depressor labii inferioris, mentalis, inferior aspect of orbicularis oris, and the risorius. The cervical branch innervates the platysma. The facial nerve innervates facial musculature on the deep surface of the muscles, except for the buccinator, mentalis, and levator anguli oris, which are innervated on the superficial surface.

The parotid fascia invests the parotid gland and this fascial layer is contiguous with the superficial layer of the deep cervical fascia, which splits and completely invests the parotid gland. Superficial to the parotid fascia is the superficial muscular aponeurotic system (SMAS), which lies between the parotid fascia and the skin. The SMAS and the parotid fascia are adherent, but a plane can be established between these two layers. Superficial to the SMAS is the subcutaneous tissue and the skin.

19.3 Evaluation of the Parotid Defect
Reconstruction of the parotid defect requires critical evaluation of the following structures:
1. Parotid gland.
2. External facial skin.
3. Facial nerve.
4. Auricle.
5. Temporal bone and skull base.
6. Mandible and maxilla.
7. Patient body habitus and body mass index (BMI).

Parotid defects can present in a variety of combinations. One patient may present with a parotid and external skin defect with an intact facial nerve, while another may present with a parotid, external skin, auricle, and temporal bone defect with facial nerve sacrifice. A customized and detailed assessment of these structures is critical to optimizing the reconstructive outcome. Broadly speaking, it is useful to characterize the parotid defect into four categories: soft tissue defect, soft tissue defect with facial nerve sacrifice, soft tissue and bony defect, and soft tissue and bony defect with facial nerve sacrifice.

19.4 Goals of Parotid Reconstruction
The primary goals of parotid reconstruction are the following:
1. Customized volume reconstruction of the soft tissue deficit with minimal ptosis.
2. Restoration of facial contour and color match of surrounding facial skin.
3. Facial nerve rehabilitation with nerve grafts, slings, and ocular procedures (tarsal strip and gold weight).
4. Maintain auricle in anatomical position and prevent ear canal stenosis.

The ideal free tissue transplant would either be a fasciocutaneous or a perforator-based transplant that would not undergo significant muscle atrophy and thus would allow for customization of the soft tissue volume reconstruction and the flexibility to shape the transplant to maintain the auricle in anatomical position. The ideal transplant would provide well-compartmentalized fat that would resist ptosis, which is critical in parotid reconstruction. The ideal transplant would provide external skin reconstruction with excellent color match to surrounding facial skin. The ideal transplant would also provide long nerve grafts that may be used for facial nerve grafting in the presence of facial nerve sacrifice. Finally, the ideal donor site would also permit two-team surgery to decrease the time under general anesthesia.
The ideal tissue flap for reconstruction of the lateral face and parotid is one that does not succumb to muscular atrophy and provides a skin paddle with a skin texture and color that matches the native skin.

19.5 Options for Microvascular Reconstruction

19.5.1 Lateral Arm

The lateral arm free flap is the authors' primary choice for free tissue reconstruction of the parotid defect (Fig. 19.1, Fig. 19.2, Fig. 19.3, Fig. 19.4). The lateral arm free flap is a fasciocutaneous free flap that is supplied by the posterior radial collateral artery. The lateral arm free flap has several reconstructive advantages that make it ideal for complex parotid reconstruction. First, the adipose within the lateral arm free flap is well compartmentalized, which allows this flap to resist ptosis. The donor site has outstanding color match to the surrounding facial skin. The fasciocutaneous flap does not have muscle and thus does not undergo subsequent muscle atrophy and loss of volume. Finally, the lateral arm donor site provides a long, vascularized nerve graft with the posterior cutaneous nerve to forearm (PCNF) (Fig. 19.5). The PCNF should be used as a vascularized nerve graft for facial nerve rehabilitation. The lateral arm free flap can also be harvested using a two-team approach if the contralateral arm is used. The ipsilateral arm can be used but the two-team approach is difficult due to proximity of the surgical teams. As a result of these advantages, the lateral arm free flap is the authors' primary choice for reconstruction of most complex parotid defects.

Fig. 19.1 (a) Radical parotidectomy and temporal bone resection defect with facial nerve preservation, reconstructed with a lateral arm free tissue transfer. (b) Bolsters are used to suspend the fat and fascia to prevent a trapdoor deformity. (c) Note that because of its well-compartmentalized fat, this flap resists ptosis. Also note that the volume of the flap that was bolstered prevents a trapdoor deformity.
One of the major advantages of the lateral arm donor site is that it provides a long, vascularized nerve graft, the PCNF, which can be used as a vascularized nerve graft for facial nerve rehabilitation.

Landmarks for harvest of the lateral arm free flap are the acromion, deltoid insertion, and the lateral epicondyle. The axis of the flap is placed along a line 1.0 cm posterior to a line from the acromion to the lateral epicondyle. Alternatively, a line can be drawn from the deltoid insertion to the lateral epicondyle. A Doppler is used to identify septocutaneous perforators along the axis of the flap. The posterior incision is made through and then undermined medially so that a cuff of adipose is harvested. The adipose is then incised down to the triceps fascia. Harvesting a cuff of adipose tissue allows the adipose to lie underneath the inset and prevent a trapdoor deformity. Subfascial dissection is then performed to the lateral border of the lateral triceps head. At this time, the septocutaneous perforators and the posterior radial collateral artery can be identified from the posterior approach and the pedicle dissection can be completed from the posterior approach, ligating branches to the triceps. The anterior incision is then made, again harvesting a cuff of adipose laterally and then incising down to the brachial fascia and brachioradialis fascia. The PCNF is identified in the fascia anterior to the lateral epicondyle, dissected, and cut distally after the branching pattern is identified if a nerve graft is required. The pedicle is then identified from the anterior approach, separating the brachioradialis and the brachial fascia from the lateral intermuscular septum. The pedicle is ligated distally, pedicle dissection is performed from the anterior approach, and the pedicle is dissected and separated from the radial nerve. The posterior cutaneous nerve to the arm, which supplies sensation to the flap, is cut proximally and released from the radial nerve, as is the PCNF. The pedicle can then be dissected proximally for additional pedicle length, retracting the lateral head of the triceps posteriorly and the deltoid anteriorly.

Inset of the flap is performed with the distal portion of the flap reconstructing the superior portion of the defect. The adipose tissue around the periphery of the fat is tucked underneath the inset to prevent pincushioning along the inset. The occipital artery as it crosses the internal jugular vein is an ideal recipient vessel in its location and vessel caliber for the lateral arm flap. The facial and superior thyroid arteries are also suitable recipient arteries, although the larger caliber facial artery make leads to a vascular mismatch. The internal jugular vein, retromandibular vein, external jugular, or facial vein can be used as a recipient vein.

### 19.5.2 Anterolateral Thigh

The anterolateral thigh (ALT) donor site is another primary donor site for parotid reconstruction. This free flap is most...
often a musculocutaneous flap, but in 13% of cases it is supplied by septocutaneous perforators. The descending branch of the lateral femoral circumflex artery most often supplies the ALT free tissue transfer. There is known variability with this donor site, as the skin can be sometimes supplied by oblique or transverse branches of the lateral femoral circumflex system.

Because its fat is less well compartmentalized, and because this donor site often requires harvest of a cuff of vastus lateralis, the ALT donor site is subject to postoperative ptosis. As this donor site is most often a musculocutaneous free flap, the surgeon must account for the volume of the flap that will undergo denervation atrophy. Volume loss from denervation atrophy can be avoided by using a perforator-based flap although dissection of the perforators makes them prone to spasm. In the authors’ experience, color match to surrounding facial skin is less ideal than the lateral arm donor site.

However, there are several advantages to this donor site. This donor site provides adequate access to donor nerves, including the lateral femoral cutaneous nerve that lies in the adipose tissue encountered along the anterior incision. Additionally, the donor site provides the nerve to vastus lateralis. This donor site also provides access to the tensor fascia lata, which can be used for static suspension of the oral commissure in cases where the facial nerve is sacrificed. This donor site allows for easy two-team harvest.

Note
The fat of the ALT flap is less well compartmentalized and therefore may be subject to postoperative ptosis. Additionally, the skin color is a poor match.

Fig. 19.5 (a, b) Patient with adenocarcinoma of the parotid gland underwent radical parotidectomy and segmental mandibular resection of the body, angle, and ascending ramus. (c) Reconstruction was completed with a parascapular osteofasciocutaneous free tissue transfer, using the lateral scapular border to reconstruct the mandible and the parascapular skin paddle to reconstruct the soft tissue deficit. Note that the volume of the soft tissue deficit would have required a second free flap if the fibula donor site was used for the mandibular defect.
Note

The ALT flap provides tensor fascia that is ideal for static facial reanimation.

Landmarks for this flap are the anterior superior iliac crest and the lateral patella. A line is drawn between these two points. The perforators are typically concentrated at the midpoint of this line and can be identified using a Doppler. The anterior incision is made through the skin, adipose, and rectus fascia. Similar to the lateral arm, a cuff of adipose is harvested to prevent a trapdoor deformity. Once the rectus fascia is incised, the rectus femoris is identified by its characteristic “chevron” or “inverted V” pattern of the muscle fibers. The rectus femoris is retracted medially and the pedicle is identified on the superficial surface of the vastus intermedius. The fascia of the flap can be retracted laterally and the perforators are visualized. Pedicle dissection of the descending branch of the lateral circumflex femoral artery is performed, up to the branch supplying the rectus femoris, which the authors preserve. The posterior incision is then made through the skin, subcutaneous tissue, and the fascia lata. If musculocutaneous perforators are present, a small cuff of vastus lateralis is harvested, and the flap can be gently lifted so that the deep surface of the pedicle dissection can be completed. Inset of the flap is similar to the lateral arm flap as discussed above.

19.5.3 Parascapular Fasciocutaneous and Osteocutaneous Flaps

The parascapular fasciocutaneous free flap provides excellent soft tissue coverage to selective parotid defects. The parascapular fasciocutaneous free flap is supplied by the descending branch of the circumflex scapular artery (CSA). This donor site provides several reconstructive advantages. The adipose on the parascapular region is well compartmentalized and resists ptosis, and color match of the parascapular donor site to surrounding facial skin is excellent. If a large composite defect exists, the parascapular osteofasciocutaneous flap can be harvested, using the lateral border of the scapula to reconstruct an associated mandibular defect (▶ Fig. 19.6).

Despite these advantages, the authors consider the parascapular free flap a secondary reconstructive option for several reasons. We perform the parascapular flap in the semilateral position contralateral to the primary tumor with the donor site prepped into the field from the beginning of the operation. Nevertheless, two-team harvest in the parascapular donor site and simultaneous parotid surgery is difficult. Furthermore, donor nerves for facial nerve grafting are not readily available at this donor site.

Note

The parascapular osteofasciocutaneous free flap provides excellent soft tissue and bone for complex defects of the parotid region.

The primary landmark of the parascapular flap is the triangular space, which can be palpated on the lateral scapular border two-fifths of the distance along the lateral scapular border. The template of the skin paddle is centered over this triangular space and the lower 270 degrees are incised. The skin paddle is elevated from inferior to superior. The latissimus dorsi is identified as it extends over the inferior border of the scapula. The separation between the latissimus dorsi and teres major are identified. Dissection proceeds from inferior to superior and the descending cutaneous branch of the CSA is identified superior to teres major. The superior incision is then completed, the teres minor is retracted superiorly and the long head of triceps is retracted laterally and pedicle dissection is completed.

19.5.4 Radial Forearm

The radial forearm free flap is a reconstructive option in patients with high BMI and/or central obesity (▶ Fig. 19.7).
Patients with high BMI in whom the primary donor sites for parotid reconstruction are too thick can have tissue at the radial forearm donor site that are suitable for parotid reconstruction. Additionally, the lateral and medial antebrachial cutaneous nerves are available for facial nerve grafting, if needed. This donor site allows an easy two-team approach. The details of this flap harvest are described elsewhere in this text.

19.5.5 Rectus Abdominis

The rectus abdominis free flap has classically been described in the literature as a primary donor site for parotid and lateral skull base reconstruction. This donor site provides ample volume of tissue but has poor skin color match to the surrounding facial skin and severe flap ptosis as the adipose tissue is poorly compartmentalized. Furthermore, unless a perforator-based flap is harvested, the flap typically contains a significant volume of muscle and this can be difficult to refine for precise volume reconstruction of the parotid and face. Thus, unless there is an extensive volume defect involving the cranial base, the rectus abdominis free flap is rarely used for parotid reconstruction.

19.6 Regional Flaps, Local Flaps, and Fat Grafts

19.6.1 Submental Island Flap

The submental island flap is a regional soft tissue flap that is supplied by the submental branch of the facial artery. While this was initially described as a pedicled or a free tissue transplant, because of its proximity to the parotid region, it is almost always used as a pedicled flap. Furthermore, if additional pedicle length is required, a “reverse flow” technique can provide greater pedicle length. This flap has even been described including vascularized bone from the inner table of mandible for midface reconstruction. Most commonly, however, the authors use this flap primarily for soft tissue reconstruction of parotidectomy and cheek defects. The submental flap provides tissue with excellent color, volume, and texture match to facial skin. The donor site can typically be advanced and closed without difficulty, particularly in older individuals. Perhaps the biggest advantage is the ability to use a pedicled flap with excellent color match and contour in a patient with a vessel-depleted neck.

Note
The submental flap provides tissue with excellent color, volume, and texture match to facial skin.

The primary disadvantage of the submental island flap is that the flap harvest requires delicate preservation of the ipsilateral facial artery and submental vessels. Most patients undergoing parotidectomy including overlying skin have advanced malignancies that also require ipsilateral neck dissection and a thorough resection of the perifacial lymph nodes that are the primary echelon drainage of the parotid gland. Furthermore, this flap does not permit a two-team surgical approach. If this flap is to be used in a two-team model, careful communication between the ablative surgeon performing the neck dissection and the reconstructive surgeon performing the submental island flap should be completed to ensure that the submental vessels are preserved.

Prior level I neck dissections often preclude the use of this flap. Heavy pathologic nodal burden is a relative contraindication. Planning neck incisions is critically important as the neck dissection and parotid incision should connect to the submental flap. The skin is pinched to assess the size of the flap that can be used and still safely close the donor site. The length of the flap is determined by the defect size and can extend contralateral to the other neck. The submental artery branches from the facial artery and courses anteriorly in level IA lateral to mylohyoid and superficial or deep to the anterior belly of the digastric. The perforators pierce the platysma and supply the...
Reconstruction of the Parotid Defect

subdermal plexus near this region. An incision is made in the submental region down to the mandible on the ipsilateral side to the vessels to be utilized. The periosteum of the mandible anteriorly in the region to elevate off to preserve the perforators to the flap. The skin is brought down until the submental artery is located. The ipsilateral anterior belly of the digastric is taken to preserve the pedicle and perforators. It is then meticulously dissected posterior to its origin off the facial artery. Mobility is obtained by freeing the pedicle from the submandibular gland and ligating the facial artery distal to the submental artery branch. A level I neck dissection can be performed at the same time. The common facial vein drains the flap and must be dissected as well. The flap is rotated posteriorly and inset into the defect.

Note

Heavy pathologic nodal burden is a relative contraindication to using the submental island flap for parotid reconstruction.

19.6.2 Cervicofacial Advancement Flap

The cervicofacial advancement flap can be used to close large cheek defects by advancing adjacent face and neck skin. This flap provides excellent color match. However, the cervicofacial advancement flap does not provide volume reconstruction of the parotidectomy defect and may result in a sunken appearance. It cannot be used when cranial base or ear canal reconstruction is required. It is also less reliable in smokers, patients undergoing neck dissection and facial artery sacrifice, and patients who will require adjuvant radiation treatment. For these reasons, this flap is rarely used for parotid reconstruction.

19.6.3 Abdominal Fat Graft

The abdominal fat graft is a good option for volume reconstruction of parotidectomy defects when the overlying skin is preserved. In these cases, harvest of abdominal fat from the left lower quadrant can be performed to provide facial symmetry and contour after parotidectomy. It is not recommended in patients who will require adjuvant radiation treatment or in patients who have already received radiation treatment.

19.7 Management of the Facial Nerve during Parotid Reconstruction

In the case of the sacrificed facial nerve, direct primary repair of the divided facial nerve should be done if tension-free repair can be performed. However, performing direct primary repair during parotid reconstruction surgery is uncommon, unless the nerve is inadvertently divided. More commonly, the extracranial distal facial nerve branches are sacrificed and the main trunk of the facial nerve is sacrificed proximally. In these cases, interposition grafts are required. Common donor nerves include the PCNF, medial and lateral antebrachial cutaneous nerves, and sural nerve. If harvest of a donor nerve in the primary surgical site is permitted, the greater auricular nerve and supraclavicular nerve can be used.

Note

Common donor nerves for facial nerve reconstruction include the PCNF, medial and lateral antebrachial cutaneous nerves, and sural nerve.

We use a two-surgeon microscope for interposition nerve grafts and perform anastomosis with interrupted 9–0 nylon sutures through the epineurium. If the proximal facial nerve stump is in the temporal bone and sutures cannot be used, tissue glue can be used for reapproximation. Similar to direct primary neurorrhaphy, a tension-free interposition graft is critical. The ideal donor nerve is a long nerve with multiple branches. This allows a tension-free anastomosis and the ability to repair multiple distal branches. The polarity of the nerve graft has not been shown to affect outcomes, and we suggest orienting the nerve graft according to its branching pattern to maximize the number of distal branches that can be anastomosed. Interposition nerve grafts should prioritize the upper division branches that innervate the orbicularis oculi to prioritize eye closure. If possible, a nerve stimulator can be used to identify those distal branches that innervate the frontalis, orbicularis oculi, zygomaticus major, orbicularis oris, and the depressor anguli oris. Those branches responsible for eye closure are always prioritized. If adjuvant radiation treatment is expected, or the patient has already received radiation treatment, an insular environment for the interposition nerve graft, such as free tissue transfer, is recommended. Additionally, recent animal studies have shown a superiority of the vascularized nerve graft over nonvascularized free nerve grafts in facial nerve outcomes further supporting the importance of an insular, vascular environment for superior outcomes.

19.8 Adjunctive Facial Nerve Procedures

19.8.1 Gold or Platinum Weight

If the upper division of the facial nerve is sacrificed, platinum weights may be used to protect the eye and prevent corneal injury. An incision is made in the supratarsal crease through the skin and orbicularis oculi muscle. A skin–muscle flap is elevated over the tarsal plate. Care is taken not to disconnect the insertion of the levator palpebrae superioris muscle to the superior aspect of the tarsal plate. The tarsal plate is exposed near the lash line so that the inferior aspect of the weight parallels the lash line. The weight is centered over the medial limbus. The 6–0 nylon sutures are placed at a partial thickness through the tarsal plate to stabilize the platinum weight. The muscle and skin layers are then closed meticulously in separate layers.

19.8.2 Static Suspension of Oral Commissure

If buccal branches of the facial nerve are sacrificed, static sling of the oral commissure may be used to provide static elevation of the upper lip. Static suspension of the oral commissure provides immediate symmetry at rest and prevents drooling.
associated with oral commissure ptosis. The authors commonly use the tensor fascia lata or the palmaris longus tendon to suspend the oral commissure.

The oral commissure is exposed either through the primary surgical site or through a separate incision along the superior and inferior vermilion border. The fascia is sutured with permanent sutures to the oral commissure. If tensor fascia lata is used, it can be cut distally so that it can be inserted into the superior and inferior fibers of the orbicularis oris. The fascia is then passed superiorly and laterally and secured to the periosteum of the zygoma. Overcorrection of the static suspension is performed to account for stretching of the tensor fascia lata or palmaris longus tendon in the postoperative period.

19.8.3 Wedge Excision of Lower Lip

If the lower division of the facial nerve is sacrificed, consideration should be given to wedge excision of the paralytic lower lip to optimize oral competence. In this technique, a full-thickness wedge excision of the paralytic lower lip is performed 1.0 cm from the oral commissure. Typically, 1.5 to 2.0 cm of denervated lower lip is excised. Meticulous multilayer closure must be performed to prevent postoperative depression of the incision line.

19.9 Conclusion

The primary goals of parotid reconstruction are to provide precise volume reconstruction to reconstitute facial contour, prevent ptosis of the reconstruction, rehabilitate the facial nerve, maintain position of the auricle, and reconstruct the ear canal. There are numerous options for reconstruction of complex parotidectomy defects, and the donor site should be selected after critical evaluation of the overlying facial skin, facial nerve, auricle, temporal bone/skull base, mandible/maxilla, patient BMI, and donor-site thickness. Meticulous reconstruction of these defects will result in meaningful functional, cosmetic, and quality-of-life benefit in these patients.

References


Note

Static suspension of the oral commissure provides immediate symmetry at rest and prevents drooling associated with oral commissure ptosis.
20 Carcinoma of the Nasal Cavity and Anterior Skull Base

20.1 Introduction

Although uncommon from a population-based perspective, sinonasal malignancies represent approximately 3 to 5% of head and neck cancers.1,2,3 There is a clear association between these tumors; the prognosis is usually poor. These lesions present similarly to several benign and inflammatory conditions; thus, a thorough understanding of appropriate workup strategies is important. In the current healthcare environment characterized by increasing awareness of healthcare costs, following a standardized patient-centered decision-making process to decide which patients with sinonasal complaints warrant further workup is of utmost importance. This chapter covers sinonasal and anterior ventral skull base malignancies, including clinical presentation and diagnosis, and delves further into the evolving approaches used to manage these devastating lesions.

20.2 Epidemiology and Etiology

Sinonasal malignancies are considered rare with an incidence of up to 10 cases per million in the United States.4 The majority of sinonasal malignancies are diagnosed in Caucasians (>80%), with no clear racial predilection and with a 2:1 male predominance.1,3,5 These malignancies most commonly present in the sixth or seventh decade of life, although there are subsets of patients who are diagnosed at much earlier ages.1 The most common primary tumor sites include the maxillary sinus and nasal cavity (these sites represent nearly 80% of lesions), followed by the ethmoid sinuses1,7,8; tumors originating from the remaining paranasal sinuses and the ventral skull base are very uncommon. Although not as comprehensively cataloged compared to other malignancies, a variety of risk factors have been identified. Notably, tobacco smokers have a greater risk for sinonasal squamous cell carcinoma (SCC),9,10 while the link with alcohol intake is less clear. Although there have been individual analyses positing a role for human papillomavirus (HPV) with sinonasal cancer, this link is not as well established compared to other head and neck sites.11,12 HPV has been implicated in the malignant transformation of benign precursors, such as inverting papilloma.13,14 Other exposures have traditionally been cited to play a role in carcinogenesis, including exposure to wood products (adenocarcinoma) and certain metals such as nickel (SCC).15,16 These risk factors are further listed in Table 20.1.

20.3 Differential Diagnosis of Nasal Cavity and Ventral Skull Base Malignancies

There is a broad differential diagnosis for nasal lesions, and further details describing presentation and workup are detailed below. It is important to exclude numerous other entities that are far more common, such as rhinosinusitis, nasal polyposis, and inflammatory disorders. Other benign and lower-grade neoplastic lesions also deserve mention in a comprehensive differential diagnosis. Inverting papilloma (IP), for example, is locally destructive and harbors a malignant transformation rate of up to 11%.13,14 Numerous studies have noted a strong association between HPV and malignant transformation of IP13,14; furthermore, even without malignant transformation, there is a significant recurrence rate for IP, exceeding 50% in some analyses depending on the extent of surgical resection.23

Among malignant lesions, SCC is the predominant histopathology. Varying by primary site, lymphoma (mature B-cell non-Hodgkin lymphoma [NHL]), adenocarcinoma, and sinonasal mucosal melanoma are the next most common pathologies.1 Adenoid cystic carcinoma (ACC) and sarcomas have also been described. Furthermore, when taking into account other malignancies likely to involve or originate from the ventral skull base, the differential diagnosis is even broader, encompassing olfactory groove malignancies (including esthesioneuroblastoma and hemangiopericytoma) as well as malignant lesions of the clivus (chordoma and chondrosarcoma). Ultimately, the definitive diagnosis of these lesions requires histopathologic examination.

Note

The evaluation of a sinonasal mass requires careful examination to rule out entities that are far more common than malignancy such as rhinosinusitis, nasal polyposis, and inflammatory disorders.

<table>
<thead>
<tr>
<th>Table 20.1 Environmental risk factors for sinonasal malignancies15,17,18,19</th>
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<tr>
<td>Human papillomavirus (malignant transformation of IP)</td>
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<tr>
<td>Leather dust</td>
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<tr>
<td>Wood dust/furniture-making/carpentry</td>
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<td>Formaldehyde exposure</td>
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<td>Smoking/tobacco</td>
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<td>Textile work</td>
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<td>Farm work</td>
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<td>Abbreviations: IP, inverting papilloma.</td>
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Note

While HPV has not been identified as a primary cause of sinonasal carcinoma, HPV has been implicated in the malignant transformation of benign precursors, such as inverting papilloma.
20.3.1 Squamous Cell Carcinoma

This is the most common histopathology and shares the same demographic characteristics as reported above for sinonasal cancers overall. As previously noted, the most common sites are the nasal cavity and maxillary sinus, followed by the ethmoid sinus (> Fig. 20.1, > Fig. 20.2). In the National Comprehensive Cancer Network (NCCN) guidelines (discussed further below), nasal cavity and ethmoid sinus cancers share the same staging guidelines and similar NCCN management guidelines. Notably, neither the NCCN nor the American Joint Committee on Cancer (AJCC) have published staging guidelines for SCC of the frontal and sphenoid sinuses. Spread to cervical lymph nodes is uncommon for nasal cavity SCC, and elective neck dissection is not typically recommended in the management of these patients. For maxillary sinus SCC, regional metastasis is more frequent than with nasal cavity SCC and elective neck dissection should be performed on a case-by-case basis. This malignancy has a tendency to lead to bone erosion and hyperostosis. One population-based analysis of over 13,000 patients noted that individuals with sinonasal SCC had a 5-year disease-specific survival (DSS) rate of 52.3%, lower than those for adenocarcinoma and mature B-cell NHL.27

Note

SCC of the maxillary sinus represents a higher risk for regional metastases than SCC of the nasal cavity. Therefore, in select cases, an elective neck dissection should be considered.

20.3.2 Squamous Cell Carcinoma Variants

Variants of SCC comprise about 7% of sinonasal SCCs. They are highly unique malignancies, each with distinct histological and clinical characteristics. Verrucous squamous cell carcinoma (VSCC), spindle cell (sarcomatoid) carcinoma (SCSC), basaloid squamous cell carcinoma (BSCC), papillary squamous cell carcinoma (PSCC), and adenosquamous carcinoma (ASC) are the five histological subtypes. The demographic characteristics (race, age, gender) of patients with these malignancies are similar to that of patients with conventional sinonasal SCC. The proportion of SCSC in the nasal cavity is smaller than that of conventional SCC. Survival is also different between variants of sinonasal SCC and conventional sinonasal SCC. VSCC and PSCC

Fig. 20.1 Preoperative axial (a) and coronal (b) CT angiography scan of a patient with a large sinonasal and ventral skull base moderately differentiated invasive squamous cell carcinoma with right optic canal and orbital apex involvement. Preoperative axial (c) and coronal (d) T1-weighted gadolinium-enhanced MR imaging of the same patient. Postoperative coronal (e) and sagittal (f) T1-weighted gadolinium-enhanced MR imaging of the patient after undergoing combined bifrontal transbasal and endoscopic endonasal approach for resection of the lesion. Asterisk depicts lesion.
have better 5-year DSS than conventional SCC (84.7% and 71.5%, respectively, vs. 52.4%), but ASC has a worse 5-year DSS (18.7%).

### 20.3.3 Adenocarcinoma

Adenocarcinomas make up 10 to 20% of sinonasal malignancies and have modestly better survival rate than SCC (62% 5-year DSS for adenocarcinoma) (▶ Fig. 20.3, ▶ Fig. 20.4). Histological subtype (intestinal type vs. salivary gland type) and grade play an important role in survival, with greater than a quarter of patients with high-grade lesions presenting with metastasis. Risk factors include chronic exposure to wood dust and working in the leather industry. Numerous series have also posited an association with colon cancer, suggesting that patients diagnosed with sinonasal adenocarcinoma be referred for screening colonoscopy.

#### Note

Adenocarcinomas make up 10 to 20% of sinonasal malignancies, and have modestly better survival rate than SCC.

### 20.3.4 Mucosal Melanoma

Unlike with sinonasal SCC, the majority of patients with sinonasal melanoma are females. Five-year DSS is worse than for other malignancies, with one population-based analysis encompassing 567 patients reporting a range of 18.2 to 36.4%, depending on anatomical location (▶ Fig. 20.5, ▶ Fig. 20.6). Patients presenting with overlapping sinus involvement harbor a grave prognosis, with a 1-year survival rate of only 54.5%. Sinonasal ACCs may demonstrate perineural spread, which occurs early in the disease process, making imaging of the cranial nerves and skull base foramina essential in patients with this diagnosis. Declining mortality in the long term may be associated with distant metastasis to the lung appearing many years after initial diagnosis.

#### Note

ACCs of the sinonasal complex are typically slow-growing, indolent tumors, which are locally destructive and have a predilection for perineural spread.

### 20.3.6 Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma (SNUC) is rare; its incidence is estimated to be 0.02 per 100,00 in the U.S. The diagnosis is more common in males (62%), and the average age of diagnosis is 57.8 years (▶ Fig. 20.9, ▶ Fig. 20.10). These aggressive malignancies are believed to arise from the nasal ectoderm of the paranasal sinuses, or from the Schneiderian epithelium. SNUC usually stains positive for neuron-specific enolase, chromogranin, cytokeratins 7, 8, and 19, and negative for S-100 and vimentin; therefore, histological staining patterns are necessary to distinguish this malignancy from similar ones. Because of its aggressive nature, SNUC’s signs and symptoms progress very quickly, sometimes in a matter of months or even weeks.
Fig. 20.3 Preoperative axial (a) and coronal (b) CT scan of a patient with a large left sinonasal and ventral skull base adenocarcinoma. Preoperative axial (c) and coronal (d) T1-weighted gadolinium-enhanced MR imaging of the same patient. Postoperative coronal (e) and sagittal (f) T1-weighted gadolinium-enhanced MR imaging of the patient after undergoing a purely endoscopic endonasal approach for resection of the lesion. Asterisks depict lesion.

Fig. 20.4 Low- (a), and high-power (b) histological photomicrographs of the tumor in ▶ Fig. 20.3 consistent with adenocarcinoma. (c, d) Postoperative nasal endoscopy of this patient after adjuvant radiotherapy treatment showing adequate healing. PNSF, pedicled nasoseptal flap.
Fig. 20.5 Preoperative axial (a) and coronal (b) CT scan of a patient with a large right sinonasal and ventral skull base mucosal melanoma. Preoperative axial (c), coronal (d), and sagittal (e) T1-weighted gadolinium-enhanced MR imaging of the same patient. (f) Preoperative coronal T2-weighted MR imaging of the patient. Asterisks depict lesion.

Fig. 20.6 (a) Preoperative nasal endoscopy of the patient in Fig. 20.5 depicting the pigmented lesion in the right nasal cavity. (b) High-power histological photomicrograph of the tumor consistent with a sinonasal mucosal melanoma. Postoperative coronal (c) and sagittal (d) T1-weighted gadolinium-enhanced MR imaging of the patient after undergoing a purely endoscopic endonasal approach for resection of the lesion.
Fig. 20.7 Preoperative axial (a) and coronal (b) CT angiography scan of a patient with a large left sinonasal and ventral skull base adenoid cystic carcinoma with intracranial and intraorbital extension. Preoperative axial (c) and coronal (d) T1-weighted gadolinium-enhanced MR imaging of the same patient. Postoperative axial (e) and coronal (f) T1-weighted gadolinium-enhanced MR imaging of the patient after undergoing a purely endoscopic endonasal approach for resection of the lesion. Asterisks depict lesion.

Fig. 20.8 (a) Preoperative nasal endoscopy of the patient in Fig. 20.7 depicting the large fleshy-appearing lesion that occupies the entire left nasal cavity. Intraoperative endoscopic photographs of the patient after resection of the lesion (b), and after initial skull base repair with acellular dermal allograft (ADA) (c). (d) Low-power histological photomicrograph of the tumor consistent with a typical sinonasal adenoid cystic carcinoma. Asterisk depicts lesion.
Fig. 20.9 Preoperative coronal (a) and sagittal (b) CT scan of a patient with an expansile bilateral sinonasal and ventral skull base undifferentiated carcinoma with intracranial and intraorbital extension. Preoperative coronal (c) and sagittal (d) T1-weighted gadolinium-enhanced MR imaging of the same patient. Postoperative coronal (e) and sagittal (f) T1-weighted gadolinium-enhanced MR imaging of the patient after undergoing combined bifrontal transbasal and endoscopic endonasal approach for resection of the lesion. Asterisks depict lesion.

Fig. 20.10 Preoperative right (a) and left (b) nasal endoscopy of the patient in Fig. 20.9 depicting the large fleshy-appearing lesion in both nasal cavities. (c) Intraoperative endoscopic photographs of the patient during resection of the lesion. (d) Histological photomicrograph of the tumor consistent with a sinonasal undifferentiated carcinoma. Asterisk depicts lesion.
Imaging studies usually demonstrate a mass encompassing multiple anatomical sites and evidence of invasion into surrounding structures. These tumors tend to be large, often greater than 4 cm. Because of their invasive nature, the margin is often poorly defined. Histological examination of the tumor usually reveals hypercellular proliferation with varied patterns including trabecular, satellite, ribbon, lobular, and organoid. Cellular infiltrate includes polygonal cells with large, round, hyperchromatic nuclei, and a high nuclear to cytoplasm ratio. Frequently, the tumor invades the lymphatics, blood vessels, or soft tissue. The prognosis for SNUC is usually poor (5-year DSS: 39%).

20.3.7 Neuroendocrine Carcinoma

Sinonasal neuroendocrine carcinoma (SNEC) comprises approximately 5% of all sinonasal malignancies; the overall incidence is estimated to be 0.015 cases per 100,000 people (Fig. 20.11, Fig. 20.12). SNEC shares many of the same features as SNUC. It can be classified into the following subtypes: typical carcinoid, atypical carcinoid, and small cell carcinoma, neuroendocrine type. Immunohistochemical staining patterns are required to distinguish SNEC from SNUC. SNEC is usually chromogranin, synaptophysin, and S-100 positive. Under the microscope, they appear to be hypercellular, contain secretory granules, and do not have rosette formation. A Surveillance, Epidemiology and End Results (SEER)-based study showed that the nasal cavity (40.8%) is the most common site, followed by the ethmoid (20.4%), maxillary sinus (18.4%), sphenoid sinus (12.9%), and frontal sinus (2%). They can be graded as well-differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III), and undifferentiated/anaplastic (grade IV). Most patients present with tumors that are grade III or worse (62.7%), and approximately 70.7% of them present at stage IV. Overall 5-year DSS is 50.8%, but survival seems to vary between specific sites. The 5-year DSS for the sphenoid sinus is the highest (80.7%), and is followed by the nasal cavity (59.2%), maxillary sinus (34.5%), and ethmoid sinus (33.0%). The grade of the SNEC has prognostic value; 5-year DSS for grade I or II SNECs (92.3%) is much higher than that for grade III (48.0%) or IV (37%). Adding radiotherapy to surgical treatment does not seem to necessarily improve survival outcomes (surgery + radiotherapy: 59.4%, surgery alone: 69% 5-year DSS). However, these results should be interpreted carefully since typically radiotherapy is given postoperatively to tumors expected to have worst prognosis.

Note

The diagnosis of sinonasal neuroendocrine carcinoma requires chromogranin, synaptophysin, and S-100 positivity.

Fig. 20.11 Preoperative coronal (a) and sagittal (b) CT scan of a patient with an expansile bilateral sinonasal and ventral skull base neuroendocrine carcinoma with marked intracranial extension. Preoperative coronal (c) and sagittal (d) T1-weighted gadolinium-enhanced MR imaging of the same patient. Postoperative coronal (e) and sagittal (f) T1-weighted gadolinium-enhanced MR imaging of the patient after undergoing a purely endoscopic endonasal approach for resection of the lesion. Asterisks depict lesions.
20.3.8 Esthesioneuroblastoma (Olfactory Neuroblastoma)

Esthesioneuroblastomas, also known as olfactory neuroblastosomas, are thought to originate from olfactory cells in the area of the cribriform plate (▶ Fig. 20.13).45,46,47,48,49,50,51,52 These tumors generally have a greater rate of cervical metastasis than other sinonasal malignancies. Adequate management of these tumors includes a formal anterior ventral skull base resection, including resection of the cribriform plate. The Kadish staging system is used for this uncommon malignancy (▶ Table 20.2). Histopathologic markers distinguishing esthesioneuroblastoma from SNUC and SNEC, a group of similar tumors, are detailed in ▶ Table 20.3.

20.3.9 Rhabdomyosarcoma

Rhabdomyosarcoma is the most common sarcoma in children. When found in the sinonasal cavities, this lesion tends to be more aggressive and portends poorer prognosis when compared to rhabdomyosarcoma in other sites. Five-year survival rates approach 50%,57 and survival is improved among patients with the embryonal histological variant compared to alveolar rhabdomyosarcoma.
The sinonasal cavity is a rare site for lymphomas; for example, sinonasal NHL makes up just 0.2 to 2.0% of cases of NHL in the Western world.58 Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of lymphoma in the Western world.58 A population-based study revealed 852 cases (from 1973 to 2009) of DLBCL in the sinonasal cavities. The average age at diagnosis was 65.8 years, and there was no gender predilection.59 Within the sinonasal cavity, the frequency of site distribution is as follows: the maxillary sinus (36.9%) is the most common, followed by the nasal cavity (34%), ethmoid sinus (8.7%), sphenoid sinus (4.1%), and frontal sinus (2.3%).59 Unlike the other sinonasal malignancies discussed, there is a limited role for surgery in the treatment of this malignancy. Surgical intervention usually has no significant role in the management of these lesions; radiotherapy is the mainstay of treatment for limited lesions, and chemoradiotherapy is preferred for advanced-stage disease. The 5-year DSS for sinonasal DLBCL has been reported to be in the region of 63.5 to 68%.27,59

Extranodal natural killer/T-cell lymphoma (ENKTL) of the sinonasal cavities is endemic to many Asian countries.27 These lymphomas typically originate from natural killer cells, but some may have T-cell origins. ENKTL was previously known as “lethal midline granuloma” due to its propensity to form necrotizing and invasive lesions in soft tissue, cartilage, and bone. Epstein–Barr virus (EBV) infection is thought to be responsible for this lymphoma, and the prognosis for patients with high EBV titers may be worse.27 The average age of diagnosis is 49.9 years. The nasal cavity (80.5%) is the most frequent location, followed by the maxillary (6.22%) and ethmoid (3.73%) sinuses.60 Sinonasal ENKTL has a much worse prognosis when compared to DLBCL; 5-year DSS is 30.9%.27 However, prognosis for ENKTL of the sinonasal cavities is slightly better than ENKTL of other sites (5-year DSS of 28.3%).27,60

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**Fig. 20.13** (a) Preoperative coronal T1-weighted gadolinium-enhanced MR imaging of a patient with a left sinonasal olfactory neuroblastoma. Intraoperative photographs showing (b) the lesion protruding though the left nasal vestibule; (c) the anterior ventral skull base defect after a purely endoscopic endonasal approach and resection of the lesion; (d) initial closure of the defect using acellular dermal allograft (ADA); and (e) placement of the vascularized pedicled nasoseptal flap over the acellular dermal allograft. (f) Histological photomicrograph of the tumor depicting rosette formation consistent with an olfactory neuroblastoma. Asterisks depict lesion.
### 20.3.12 Chordoma

Derived from the notochord formed during embryogenesis, chordomas of the clivus are low-grade malignancies with metastatic potential (▶ Fig. 20.14, ▶ Fig. 20.15). Because of the intimate proximity of the clivus to posterior fossa contents, including brainstem structures as well as the sixth and other cranial nerves, these patients often present with neurologic deficits. Five-year survival rates of clival chordomas have been reported to be 65%.61

### 20.3.13 Chondrosarcoma

Arising from endochondral cartilage, skull base chondrosarcomas most commonly occur in the clivus, representing the second most common clival malignancy. They present similarly to chordoma but are more likely to be located in a paramedian position (rather than midline like chordomas), and have a better survival rate (5-year survival of 90%) (▶ Fig. 20.16, ▶ Fig. 20.17).62,63

### 20.3.14 Hemangiopericytoma

Sinonasal hemangiopericytoma (SN-HPC) is a rare vascular sarcoma that makes up approximately one-fifth of all head and neck HPC (▶ Fig. 20.18, ▶ Fig. 20.19). The nasal cavity is the most common, and the ethmoid sinus is the second most common isolated location.64 However, a systematic review by Dahodwala et al in 2013 suggests that about half of SN-HPCs are in multiple locations. The average age of diagnosis is about 51.8 years, and the distribution is about equal among both genders. Histologically, these sarcomas appear as monomorphic spindle-shaped cells with eosinophilic cytoplasm and show little mitotic activity. As the name suggests, the cells of the tumor usually surround small blood vessels. They stain positive for actin and vimentin. There is a high recurrence rate.65,66,67,68 Grading of the SN-HPCs is divided into three groups: low-grade ones have spindle-shaped cells with little crowding of blood vessels as well as little to no mitotic figures; intermediate-grade sarcomas have increased mitotic activity; and high-grade sarcomas have significant mitotic activity and necrosis.

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**Note**

ENKTL of the sinonasal cavities is endemic to many Asian countries.

**Note**

Chondrosarcomas are likely to be located in a paramedian position (rather than midline like chordomas), and have a better survival rate.
Fig. 20.15 Intraoperative endoscopic images of the patient in Fig. 20.14 with the clival chordoma during the endoscopic endonasal approach (a), resection (b), and final brainstem decompression (c). (d) Postoperative endoscopic image of the sinonasal cavity after the resection bed has healed.

Fig. 20.16 Preoperative axial (a) and sagittal (b) CT scans of a middle-aged woman with a large paramedian clival chondrosarcomas. Preoperative axial (c) and sagittal (d) T1-weighted gadolinium-enhanced MR imaging of the patient showing significant heterogeneity in the lesion. Postoperative axial (e) and sagittal (f) T1-weighted gadolinium-enhanced MR imaging of the patient after endoscopic resection of the lesion. Asterisks depict lesion.
ones usually compress some portion of vessels; high-grade ones compress vessels entirely.69

**Note**

Sinonasal hemangiopericytoma is a rare vascular sarcoma that occurs most commonly in the nasal cavity.

### 20.3.15 Metastasis

Metastases to the sinonasal tract and anterior ventral skull base are exceedingly uncommon, but should be included as part of a broad differential diagnosis for lesion of this location (Fig. 20.20). Breast cancer and renal cell carcinoma have been noted to metastasize to the ventral skull base.70,71 Furthermore, distant metastases to the sellar region have also been reported,72 and should prompt workup for a variety of visceral malignancies including lung cancer.73,74 There has been debate as to the role of surgical intervention for sellar metastases, and there is currently no definitive consensus regarding appropriate management.75

### 20.4 Staging

Staging systems provide important guidance for management approaches and prognosis. Creation of an effective staging
system for sinonasal and ventral skull base malignancies presents unique challenges due to the heterogeneous nature of pathologies. Although a variety of staging systems have been proposed, the AJCC staging represents the most widely used system for sinonasal cancer in contemporary practice (▶ Table 20.4a, b). There are minor differences in staging based on primary sinonasal site. As opposed to staging schema for other head and neck malignancies, T staging is based on the invasion of anatomical structures and locations rather than overall tumor size. Five-year survival rates greater than 60% for early-stage sinonasal lesions are halved upon consideration of stage IV lesions. These vary significantly depending on the specific cancer histopathology discussed. For example, esthesioneuroblastoma has been noted to have clinical behavior that is substantially different from many other sinonasal malignancies, including a greater propensity for cervical metastasis. Consequently, additional staging systems have been developed and are used for this uncommon malignancy. Although not a malignant tumor per se, IP can undergo malignant transformation in a subset of cases, and the Krouse staging system has been developed in an attempt to facilitate appropriate surgical planning and management (▶ Table 20.5).
20.5 Clinical Presentation

Sinonasal malignancies present a challenging clinical dilemma. Early diagnosis may be lifesaving, as advanced lesions harbor dismal prognoses. However, signs and symptoms mimic inflammatory etiologies such as rhinitis and rhinosinusitis, which are far more prevalent. Hence, maintaining an adequate index of suspicion, performing a thorough endoscopic examination, and pursuing appropriate diagnostic inquiry are all important considerations.

A patient consultation should include all of the queries encompassing a comprehensive head and neck history, with focus on eliciting information relating to nasal obstruction, rhinorrhea, purulent drainage, epistaxis, allergy complaints, and pain. The presence of unilateral symptoms, unexplained epistaxis, and complaints possibly related to cranial neuropathies (such as visual disturbances and facial paresthesias) should raise the index of suspicion and increase the likelihood of obtaining diagnostic imaging. Additionally, information related to constitutional symptoms should be taken into account, as well as an occupational exposure history (> Table 20.1).

Table 20.4 American Joint Committee on Cancer T staging for sinonasal squamous cell carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus, except extension to the posterior wall of the maxillary sinus and pterygoid plates</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades any of the following: bone of the posterior wall of the maxillary sinus, subcutaneous tissues, floor or medial wall of the orbit, pterygoid fossa, or ethmoid sinuses</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderate advanced local disease. Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribiform plate, frontal or sphenoid sinuses</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor limited to the larynx with vocal fold fixation and/or inner cortex of the thyroid cartilage</td>
</tr>
</tbody>
</table>

Table 20.5 Krouse’s classification for inverted papilloma78

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Confined to nasal cavity</td>
</tr>
<tr>
<td>T2</td>
<td>Ethmoid sinuses, medial maxillary sinus, ostiomeatal complex</td>
</tr>
<tr>
<td>T3</td>
<td>Maxillary sinus wall other than the medial wall, sphenoid/frontal sinus</td>
</tr>
<tr>
<td>T4</td>
<td>Extra-sinonasal extension (orbit, intracranial, pterygomiandepalay) or concurrent malignancy</td>
</tr>
</tbody>
</table>

20.6 Diagnosis and Workup

20.6.1 Physical Examination

In addition to a thorough head and neck physical examination with emphasis on anterior rhinoscopy, oral cavity evaluation, assessing for the presence of middle ear effusion, and a cranial nerve evaluation, any patient presenting with nasal complaints
should undergo in-office nasal endoscopy (► Fig. 20.2). Although there are few studies quantifying the efficacy of nasal endoscopy as a “screening” tool, the downside of missing an early-stage lesion makes performing such an examination essential. The nasal endoscopic examination should carefully evaluate the nasal floor, septum, middle meatus, lateral nasal wall, and the paranasal sinuses when feasible (such as in patients who have had prior sinus surgery). The presence of any masses, lesions, or ulcers should be noted. In patients with masses appearing to be benign polyps, a short course of medical intervention with topical and/or systemic steroids can be attempted to see if there is a response; however, surgical intervention with collection of tissue for pathologic analysis is ultimately required unless these lesions regress completely. In any suspiciously appearing lesions that suggest the need for biopsy, imaging (see below) is usually warranted unless the entirety of the mass can be viewed within the nasal cavity, in order to ensure that there is neither intracranial extension or ventral skull base connection (i.e., encephalocele).

In addition to the considerations described above, examination should include evaluation of the neck, as a small proportion of patients presents with positive lymph node disease. This figure varies by specific primary site and histological subtype, but nodal involvement is typically noted in fewer than 10% of patients with sinonasal malignancies overall. The examiner should also evaluate for a neurologic examination that includes testing for decreased/absent sensation in the distribution of the trigeminal nerve branches, particularly V2 and V3, as well as the presence of ocular abnormalities such as proptosis and deficient extraocular muscle movement.

**20.6.2 Imaging**

Among patients in whom there is suspicion of a sinonasal malignancy, understanding the appropriate imaging modalities to pursue is of great importance. Fine-cut computed tomography (CT) scans play an integral role and often represent the initial modality ordered in current practice. CTSs are excellent for defining the extent of bony involvement, including the relationship of lesions to critical orbital, intracranial, and ventral skull base structures. Orbital structures, including orbital bone, the orbital fissures, and the optic foramen may exhibit expansion on CT, strongly supporting the possibility of tumor invasion. CT is an important tool for surgical planning, and is often used in conjunction with intraoperative image guidance systems.

Magnetic resonance imaging (MRI) is optimal for detailing non-bony structures. For example, various MR sequences can be helpful in differentiating between soft tissue structures and the presence of fluid. Furthermore, in the context of sinonasal and ventral skull base malignancies, MRI is important in determining the presence of dural invasion; gadolinium-enhanced images can be useful in this respect. Like CT, MR can also be used intraoperatively for image guidance purposes, more commonly in cases with extensive skull base and intracranial involvement. Additionally, the combination of CT with positron emission tomography (PET) has shown value in the setting of residual and recurrent disease for identification of regional involvement, distant metastasis, and distinguishing malignant from nonmalignant tissue. Further studies are needed to elucidate the utility of PET/CT in the evaluation of sinonasal malignancies. The value of routine PET/CT for newly diagnosed early-stage disease is unclear. It is important to note that the NCCN guidelines do suggest consideration of PET/CT in the evaluation of stage III or IV disease.

Conventional angiography has been historically valuable for detailing the relationship of lesions to vascular structures, including the internal carotid artery. In recent years, noninvasive variants, including CT and MR angiography, have gained favor and are being increasingly used. Information derived from these images help the operating surgeon determine optimal approaches, as well as determining whether supplementary procedures may need to be considered (e.g., revascularization due to sacrifice of a major vessel).

### 20.7 Management

#### 20.7.1 NCCN Guidelines

Familiarity with the NCCN guidelines for management of sinonasal malignancies is important for practitioners involved in the care of these patients. Although a complicated algorithm exists, one way of approaching this can be to approach early-stage lesions with single-modality treatment, and reserve multimodality treatment for early-stage lesions with additional risk factors and advanced-stage lesions. For most maxillary sinus tumors, T1/2 N0 disease should be managed with surgical resection, followed by close follow-up if margins are negative. Further surgical re-resection should be considered for positive margins (when possible), with consideration of adjuvant radiotherapy even after a negative margin re-resection. Perineural invasion, and positive margins even after re-resection mandate consideration of either radiotherapy, or chemoradiotherapy. For T3/T4aN0 maxillary sinus lesions, primary surgical resection followed by adjuvant therapy is the recommended approach within the NCCN guidelines. T4b lesions warrant definitive radiotherapy, systemic chemoradiotherapy, or inclusion in a clinical trial. The presence of any positive lymph nodes necessitates treatment of the neck, optimally via neck dissection rather than radiotherapy. The absence of any adverse features from the neck dissection specimen, including positive margins or extracapsular nodal spread, only warrants adjuvant radiotherapy to the primary and neck; however, the presence of any of these adverse features should prompt consideration of adjuvant chemoradiotherapy rather than radiotherapy alone. The guidelines above are specific to maxillary sinus malignancies; the
Carcinoma of the Nasal Cavity and Anterior Skull Base

NCCN also describes an algorithm for approaching ethmoid sinus malignancies that is largely similar, with one key difference being the consideration of definitive radiotherapy for management of the primary lesion, although surgical resection is still preferred.

20.7.2 Surgical Treatment

Overview of Traditional Surgical Approaches versus Endoscopic Resection

Although open surgical approaches have been historically employed in the management of sinonasal and ventral skull base malignancies, technological advances have facilitated an increasing popularity of minimally invasive techniques over the past two decades. The decision of whether to consider an open, endoscopic, or combined approach is dependent on numerous factors, including the primary site, extent of disease, and surgeon experience.85 Historically, en bloc resection has been suggested to be necessary to achieve an oncologically sound resection, although there has never been any evidence definitively supporting this assertion. Furthermore, numerous analyses have noted the ability to obtain negative margins as a far more important consideration.86 Accordingly, multiple analyses have noted similar outcomes in patients undergoing endoscopic tumor resection compared to open approaches. In a retrospective study encompassing 66 patients with malignant anterior ventral skull base malignancies, Eloy and colleagues noted that patients managed with transnasal endoscopic resection had equivalent complication rates and survival compared to those who underwent craniofacial resection.87 One significant difference noted was a lengthier hospital stay and higher recurrence rates among patients who underwent craniofacial resection compared to patients managed purely endoscopically, highlighting the increased morbidity and challenging postoperative course of the former approach. In a later and larger study by the same group, similar findings were noted.88 However, these findings should be carefully interpreted, as selection bias usually caused smaller ventral skull base malignancies to be treated with the endoscopic approach, and much larger lesions with inherently poorer prognoses to be treated with the open approaches.

Regardless of tumor involvement, several anatomical structures should be examined when reviewing imaging preoperatively. Within the sphenoid sinus, a present Onodi cell may envelop the optic nerve89,90,91; bony dehiscence over the optic nerve and the internal carotid artery should be recognized, as these occur relatively frequently. The integrity of the lamina papyracea, the attachment of the uncinate bone, and the presence and location of an extracranial anterior ethmoid artery should also be noted on preoperative imaging. Importantly, when necessary during surgery, the anterior ethmoid artery should be divided closer to the cribiform plate to prevent retraction into the orbit leading to hematoma. Furthermore, the presence of agger nasi cells, suprabullar cells, and frontal cells should be noted if frontal sinusotomy is anticipated.92 The surgeon should also be familiar with the depth of the olfactory fossa, as classified by Keros. Specifically, this classification refers to the length of the lamina lateralis, as type 1 Keros (1–3 mm) and type 2 Keros laminae (4–7 mm) suggest lower risk than a type 3 lamina lateralis (≥8 mm). Patients with a Keros type 3 configuration may be at risk for disruption of the lamina lateralis intraoperatively.90,93,94

Endoscopic Resection of Sinonasal Malignancies

Resection of masses emanating from the nasal septum, lateral nasal wall, or the paranasal sinuses can be performed successfully endoscopically. Much like open interventions, endoscopic approaches vary widely based on the location and extent of the lesion. Unlike open approaches, en bloc resection is far less frequently accomplished, increasing the necessity of repeated frozen sections to maximize the chances of adequate resection with negative margins.

The surgical steps for addressing an anterior ventral skull base malignancy vary significantly based on the structures involved and a lesion's location.95,96 Briefly, any visualized intranasal lesion can be debulked using a microdebrider. Mucosa overlying the nasal septum should not be disrupted (when feasible) in order to allow for subsequent use of a nasoseptal flap for reconstruction in appropriate cases. A maxillary antrostomy as well as a total ethmoidectomy may be performed. To reach the skull base, the sphenoid sinus is found and a sphenoidotomy may be performed, with care taken during all steps to preserve nasoseptal mucosa. After an adequate sphenoidotomy is performed, the intersinus septum may be addressed, and the optic nerve and internal carotid arteries are identified. In cases with lesions extending to the frontal sinuses, an extended Draf III frontal sinusotomy (modified Lothrop procedure) or modified subtotal Lothrop procedure may be performed, and posterior table of the frontal sinus identified.97,98 Ventral skull base resection may encompass removal of the cribiform plates, crista galli, olfactory bulbs, fovea ethmoidalis, as well as endoscopic resection of involved dura.

Open Surgical Intervention

Specific surgical steps differ based on the site and extent of the lesion. An exhaustive review of specific operative steps is beyond the scope of this analysis, and best learned by review of available surgical atlases. Nonetheless, important surgical principles are detailed below.

Note

Irrespective of the surgical approach (endoscopic or open), numerous analyses demonstrate that negative margins are paramount.

Anatomical Considerations for Performing a Safe Endoscopic Surgery

The involvement of critical structures dictates the extent of surgical intervention. Involvement of the orbit, pterygopalatine fossa, infratemporal fossa, cavernous sinus, and other skull base structures all alter surgical planning. Recognizing extension to these structures is critical in formulating a surgical plan. Furthermore, detailed anatomical evaluation of imaging is also important for safely performing surgery.
The nomenclature associated with various types of maxillectomies is in relation to the location of the infraorbital nerve (V2). Lesions limited to the lateral nasal wall and medial wall of the maxillary sinus may be amenable to a medial maxillectomy. Though smaller lesions can be addressed endoscopically, in the context of an open procedure, a lateral rhinotomy incision or midfacial degloving approach is performed to access this location, followed by exposure and removal of the maxillary sinus wall medial to the infraorbital nerve.99 For lesions involving the hard palate, an inferior maxillectomy may be an optimal approach; this procedure can employ midfacial degloving or a sublabial approach. Tumors requiring a total maxillectomy generally require a lateral rhinotomy incision in combination with a lip-split, as well as intraoral incisions (including separation of the hard palate from the soft palate) (▶ Fig. 20.21).

Depending on the extent of orbital involvement, orbital exenteration may also be required; considerations specific to orbital extension are further discussed later in the chapter. Lesions involving the anterior ventral skull base, most commonly extension from nasal cavity/ethmoid/maxillary sinus carcinoma, or esthesioneuroblastoma, may warrant extensive resection in complicated locations, including the cribiform plate and fovea ethmoidalis. These tumors, along with sinonasal malignancies involving the middle cranial fossa, may require craniofacial approaches for appropriate access.100 These approaches may involve considerable morbidity and mortality, and are performed in conjunction with neurosurgery. Depending on the specific tumor site, craniofacial resection usually encompasses a bicoronal incision and elevation of a pericranial flap for use in subsequent reconstruction. Tumor pathology and location dictate the location of subsequent osteotomies and the remainder of the procedure.

Rehabilitation of Maxillectomy Defects

A variety of options can be considered for the reconstruction of maxillectomy defects. Although a comprehensive discussion of these techniques, which range from plating and primary closure to free flap reconstruction, are beyond the scope of this chapter and are discussed elsewhere in this text, rehabilitation of maxillectomy defects using prosthetics remains an underappreciated approach. Importantly, interdisciplinary cooperation and preoperative consultation with a maxillofacial prosthodontist is a significant consideration. For patients who will require a prosthesis, discussion of which structures to preserve is imperative. Preservation of as many teeth as possible is important for improving rehabilitative potential, particularly cuspsids and teeth posterior to the cuspsids.101 Intraoperatively, bone cuts should be performed as far away from preserved teeth as possible to maximize remaining supporting bone. An additional important point is that preservation of as much of the hard palate as possible is beneficial for postoperative function.

Note

Lesions involving the anterior ventral skull base, including the cribiform plate and fovea ethmoidalis, may benefit from craniofacial approaches for appropriate access.

Note

When considering oral rehabilitation, preservation of as much of the hard palate as possible is beneficial for postoperative function.
Skull Base Reconstruction

Reconstruction of ventral skull base defects following open surgical resection can encompass options from all aspects of the reconstructive ladder. These techniques are further discussed in a dedicated chapter in the text, but a general overview is given below. The optimal reconstructive strategy depends on numerous factors, including the size and location of the defect. Vascularized pedicled grafts are preferred, as their use minimizes problems with wound healing.\(^{102}\)

For many ventral skull base defects from open resection, the vascularized pericranial flap is the workhorse of reconstruction. A bicoronal flap is usually raised carefully in order to facilitate harvest of the pericranial flap, and parallel paramedian incisions in the scalp periosteum are made near the temporalis muscles. The supraorbital and supratrochlear arteries are the blood supply to this flap. Alternatively, a temporoparietal fascia flap may be considered for reconstruction of these ventral skull base defects from open resection.

The vascularized pedicled nasoseptal flap is an important reconstructive option in endoscopic resections. Multilayer closure is currently more often used for adequate ventral skull base repair and minimizes the chances of postoperative cerebrospinal fluid (CSF) leaks. Many variations of the pedicled nasoseptal flap have been described over the past decade.\(^{103,104,105,106,107,108,109,110,111,112,113}\)

Regardless of specific technique used, avoidance of pedicle disruption is important for success. In our institutions, autologous fat and/or autologous fascia lata, or acellular dermal allograft or Alloderm (LifeCell Corporation; Branchburg, New Jersey) are deployed as inlay grafts in cases with a dural defect. After this, an absorbable packing material such as Surgicel is placed, followed by placement of our pedicled nasoseptal flap. It is especially important to place the mucoperichondrial portion of the nasoseptal flap facing the ventral skull base defect.

### Additional Anatomical Considerations

#### Pterygopalatine Fossa and Infratemporal Fossa Involvement

Tumor extension into the pterygopalatine fossa (PPF) and infratemporal fossa (ITF) has traditionally been managed with radical resection utilizing open approaches. An anterior craniofacial resection can be expanded to include these structures in an en bloc resection. In recent years, multiple cadaveric studies, radiologic analyses, and case series have demonstrated the feasibility of the endoscopic approach to these regions,\(^{114,115,116,117,118}\) although there remains a paucity of high-quality large series comparing outcomes of endoscopic and open approaches.

#### Management of the Cavernous Sinus

Although involvement of the cavernous sinus previously signified unresectable disease, there are an increasing number of institutions in which select patients may undergo cavernous sinus resection. Cavernous sinus involvement may present with a number of sequelae, including visual abnormalities or cerebrovascular accident (CVA). Although a handful of cases with cavernous sinus involvement result from metastasis or extension through bony fissures and foramina, the vast majority of cases stem from direct extension.\(^{119}\) Open techniques involving craniotomies have been historically performed for these lesions, although endoscopic approaches have been increasing in frequency. Importantly, evaluation of preoperative imaging, including angiography, is mandatory prior to any surgical intervention; the integrity and involvement of the internal carotid artery should be assessed. Although resection of the intracavernous carotid significantly increases the risk of CVA, revascularization procedures may be planned in an attempt to reduce this risk.\(^{120,121,122}\)

### Management of the Orbit

Orbital involvement engenders additional morbidity through a variety of mechanisms.\(^{*}\) Nearly 50% of patients with sinonasal malignancies present with orbital involvement,\(^{123,124}\) Surgical intervention is recommended in these cases; malignancies adjacent to but not invading orbital bone may be addressed by resecting the bone, and require multiple intraoperative frozen sections to confirm negative margins. Instances in which there is further involvement, including involvement of the periorbita, may require orbital exenteration. While some surgeons feel that breach of the periorbita, which acts as a barrier, necessitates orbital exenteration, others advocate resecting the periorbita and extraconal fat and assessing whether the cuff of fat resected is negative on frozen-section pathology. There is no definitive consensus regarding which approach is optimal, and it is dependent on multiple factors, including surgeon preference.

Nearly 50% of patients with sinonasal malignancies present with orbital involvement, a finding that decreases survival by as much as half.\(^{123}\) Increasing the necessity of multimodality therapy.

### Clival Lesions

As the bony structure separating parasellar structures and the nasopharynx from the posterior fossa, there are a variety of considerations in determining the optimal approach to the clivus.\(^{125,126,127}\) On preoperative evaluation of imaging, the upper portion of the clivus can be found behind the sphenoid sinus...
and sellar floor. A majority of lesions in this area are chordomas (Fig. 20.14, Fig. 20.15), which despite their name are considered malignancies due to their propensity for invasion and metastatic potential; these lesions usually originate in the midline. The next most common clival malignancy, chordomas (Fig. 20.17, Fig. 20.16), should be suspected if imaging reveals a paramedian lesion. The close proximity of critical neurovascular structures, including the basilar artery and brainstem, makes a comprehensive understanding of the surrounding anatomy important before consideration of surgical resection. Much like for ventral skull base malignancies in other locations, skull base centers have been increasingly adopting an endoscopic approach for removal of these lesions. Adequate visualization of the vidian nerve is of paramount importance intraoperatively, as this can be used as a landmark to stay below the internal carotid artery and prevent injury to this major artery.

20.7.3 Nonsurgical Treatment

Radiotherapy

The majority of resectable advanced lesions are managed with multimodality therapy, specifically through surgical resection followed by adjuvant radiotherapy. In contrast, nonsurgical candidates, including individuals with unresectable disease, often undergo radiation therapy or chemoradiotherapy; these patients experience poorer outcomes. NCCN guidelines for postoperative radiation therapy have been briefly reviewed above, and include extensive lesions as well as pathology revealing other risk factors. The advent of intensity-modulated radiotherapy (IMRT) has heralded an era of decreased complication profiles, as this approach allows for more precise planning and administration of radiation.

Although surgery is the preferred modality for nasal cavity and ethmoid sinus tumors, definitive radiotherapy can be employed in early-stage tumors, with 5-year survival rates exceeding 90%. In nonsolid malignancies, such as lymphomas, radiotherapy plays a primary role in achieving remission, and has been suggested to be more effective than primary chemotherapy in some lymphomas.

Chemotherapy

Although there have been significant advances in the efficacy of chemotherapeutics for other malignancies, there have been few targeted therapies developed in recent decades for head and neck malignancies, and none specifically for sinonasal and ventral skull base lesions. Studies in the 1980s found that cisplatin and 5-fluorouracil (5-FU), have been in existence for more than four decades. There has been increased interest in biological agents specifically targeting molecular pathways, such as the U.S. Food and Drug Administration (FDA) approval of cetuximab for head and neck cancer in 2006, although much work remains to be done to elucidate their utility in sinonasal malignancies.

Outside of the setting of palliative treatment, systemic chemotherapy is not used as monotherapy for sinonasal and ventral skull base malignancies. Rather, these agents are mainly employed as neoadjuvant or adjuvant treatments, or within concomitant chemoradiotherapy regimens. One 2003 trial in 49 patients with resectable sinonasal lesions employed cisplatin and 5-FU, noting a 3-year survival exceeding 65%; patients received this regimen followed by surgical resection and radiotherapy. Importantly, there were two deaths, as well as numerous other individuals sustaining cardiac toxicities.

Note

Outside of the setting of palliative treatment, systemic chemotherapy is not used as monotherapy for sinonasal and ventral skull base malignancies.

Future Nonsurgical Therapies: Biological Agents

As chemotherapeutics employed today are largely the same agents used four decades ago, finding alternative systemic treatments remains an unmet clinical goal. Recently developed immune therapies have offered a promising alternative to current treatments. As there is a preponderance of literature demonstrating deficient antitumor immune surveillance mechanisms in cancers, several antibodies and biological agents have been studied in recent years. Ipilimumab (anti-CTLA4 antibody), pembrolizumab, and nivolumab have been approved for use in unresectable and metastatic melanoma in recent years. The latter two are checkpoint inhibitors, interfering with the programmed death receptor ligand (PD-1) present on T cells. Modest but improved survival rates in these subsets of patients have been noted. Furthermore, nivolumab was noted to increase survival among patients with recurrent and metastatic head and neck SCC, earning a FDA breakthrough therapy designation in 2016 as a result.

20.8 Complications of Treatment

20.8.1 Surgical Complications

The intimate proximity of critical structures surrounding the sinonasal contents and ventral skull base underlies the significant risk of complications associated with therapy. A brief discussion of complications can be organized by location, including intracranial, orbital, and nasal complications.

Depending on the specific lesion encountered and surgical intervention performed, several critical orbital structures can be compromised, including the optic nerve and extraocular muscles. Interference with these structures may result in visual acuity deficits and diplopia. Enophthalmos is another possibility after orbital surgery. During performance of an enucleation or exenteration procedure, inadvertent globe rupture can result in sympathetic ophthalmia, a delayed antibody-mediated immune response to the contralateral eye, ultimately resulting in blindness. If there is concern for this complication, prompt ophthalmology consult and administration of immunosuppressants such as corticosteroids should be considered.

Intracranial complications can occur both during the neurosurgical and otolaryngologic portions of a procedure. In addition to the general risks of hemorrhage from penetration of the brain parenchyma and the risk of postoperative pneumocephalus, the risk of CSF leaks due to inadequate repair of ventral
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skull base defects remains significant. Hence, in any postoperative patient in which there is clear salty-tasting rhinorrhea, comprehensive endoscopic examination, consideration of intrathecal injection to identify a skull base defect, and sending specimens for β₂ transferrin testing are important steps. Furthermore, imaging modalities such as CT cisternography have been suggested by some as helpful for identification of skull base defects. Lastly, the authors advocate consideration of returning to the operating room for exploration in postoperative patients with CSF rhinorrhea. Although routine antibiotic prophylaxis in this setting remains controversial, failure to address CSF rhinorrhea can lead to meningitis and/or intracranial abscesses.

20.10 Clinical Cases

20.10.1 Case 1

T4aNOM0 malignant melanoma of the right sinonasal cavity.

Clinical Presentation

The patient is a 62-year-old man who presented with daily unilateral epistaxis from the right nostril for about 6 months.

Physical Examination

Rigid endoscopic nasal examination (Fig. 20.6a) revealed a fleshy pigmented mass in the right nasal cavity. The mass was causing complete obstruction of the right nasal passage and deviation of the nasal septum toward the left. The mass appeared fleshy and hypervascular. The cranial nerve examination was normal, except for a subjectively decreased sense of smell.

Diagnosis and Workup

The patient underwent both CT and MRI, which demonstrated an enhancing neoplasm in the superior aspect of the right nasal cavity with extension into the right ethmoid air cells abutting the cribriform plate and fovea ethmoidalis, with no gross evidence of intracranial extension (Fig. 20.5a–f). There was probable disease adjacent to the dorsal aspect of the left middle turbinate and dorsal aspect of nasal septum with extension into the nasopharynx. There was complete opacification of the right sphenoid sinus, likely from obstructed secretions. The patient was taken to the operating room to perform a biopsy and tumor debulking, with a plan for definitive management pending final pathology.

The biopsy revealed mucosal melanoma. The diagnosis was supported by positive staining for S-100, vimentin, HMB-45, Melan-A, and Fontana stain. There was focal positivity for CD56 and p53. Stains for CK7, CK20, desmin, MyoD1, NSE, CD2, p63, CD20, and Prussian blue were negative in tumor cells. The patient underwent a staging CT, MRI, and PET scan. The PET scan demonstrated postsurgical changes, no abnormal uptake or mass lesion in the right nasal cavity, and almost complete opacification of the right ethmoidal and bilateral sphenoidal sinuses. There were two small foci of moderate uptake of standardized uptake value (SUV) 4.0 within the anterior and posterior right ethmoids. There was no evidence of regional or distant metastases.

Options for Treatment

The mainstay of management for sinonasal mucosal melanoma is surgical resection with negative margins. In this patient with no evidence of regional metastasis, there is no role for elective neck dissection. The role of sentinel node biopsy has not been established. Although, the role of adjuvant radiotherapy has been debated, the rate of local control seems to be improved, while overall survival may not be affected. Chemotherapeutic options are typically reserved for palliation. Immunotherapy may be beneficial for a select group of patients.

20.9 Conclusion

Sinonasal and ventral skull base malignancies harbor a significant potential for devastating sequelae due to the close proximity of critical intracranial, orbital, and neurovascular structures. These malignancies present unique diagnostic challenges, due to the similar presentation of more common benign inflammatory sinonasal disorders. Management strategies employed often cause significant functional disturbance, contributing to significant risks for morbidity and mortality.
Treatment of the Primary Tumor

After completing the staging workup, the patient returned to the operating room for an endoscopic endonasal approach to the anterior ventral skull base that included a wide maxillary antrostomy, resection of the superior and middle turbinates, total ethmoidectomy, and right frontal sinusotomy. The tumor appeared to arise from the middle and superior turbinates. A portion of the medial septal mucosa was also removed for wide margin excision. Several biopsies were taken from the margins, which were all negative. The right cribriform was then resected. This resulted in a right cribriform bony defect with some dural tears and a high-flow CSF leak. It was felt that the dura did not need to be resected in this case because the tumor had not eroded through the bony skull base.

A gross total resection of the tumor was performed. Secondary repair of the anterior ventral skull base dural defect was performed using a multilayer repair technique. A thin layer of acellular dermal allograft was placed through the dural defect to plug up the fistula. A second layer of acellular dermal allograft was placed as an onlay graft and tucked underneath the bone. A pedicled nasoseptal flap from the inferior portion and floor of the right nasal cavity was then rotated to buttress the anterior ventral skull base defect.

Adjuvant Treatment

The patient was referred to radiation oncology for adjuvant radiation therapy. Final surgical pathology revealed a gross total resection of the tumor with negative margins. He received a course of adjuvant radiation therapy to the right sinonasal cavity. Radiation treatment delivered 6,000 cGy to the right nasal cavity in areas of high risk treated with IMRT. The elapsed time was 39 days. He completed the entire prescribed dose without any significant treatment breaks. During radiation treatment he experienced radiation dermatitis with some erythema of the treated region.

Summary of Treatment

The patient was treated with complete surgical resection via an endoscopic endonasal ventral skull base approach for a T4aN0M0 mucosal melanoma of the right sinonasal cavity. The skull base was reconstructed with an acellular dermal allograft and a pedicled nasoseptal flap. There was no evidence of regional or distant metastasis. The patient received postoperative adjuvant radiotherapy to the right nasal cavity. The patient is now 3 years postoperative with no evidence of recurrent disease.

20.10.2 Case 2

Left nasal cavity esthesioneuroblastoma Hyams’ grade 2, Kadish’s stage A.

Clinical Presentation

A 53-year-old woman presented with unilateral left-sided nasal obstruction, intermittent epistaxis, and a mass protruding from the left nostril. The patient was initially seen by an otorhinolaryngologist, who performed a biopsy of the mass and referred the patient to a neurosurgeon for definitive management. However, the patient did not follow-up. Her symptoms progressed over the course of approximately 1 year before she sought medical attention at our institution.

Physical Examination

The patient had a fleshy polyoid mass protruding from the left nostril (> Fig. 20.13b). The mass completely obstructed the nostril and prevented endoscopic examination of the left nasal cavity. Endoscopic examination of the right nasal cavity was normal, except for deviation of the nasal septum to the right. The patient’s neurologic examination was unremarkable and notably the extraocular movements appeared intact and sensation in the distribution of the trigeminal nerve was normal.

Diagnosis and Workup

The pathology obtained from the original biopsy was consistent with an esthesioneuroblastoma, Hyams’ grade 2. The diagnosis was supported by strong positive staining for chromogranin, synaptophysin, NSE, and focal staining for S-100 protein. Stains for p63, pankeratin, and CD99 were negative. An MRI of the paranasal sinuses was ordered and demonstrated a large intensely enhancing heterogeneous mass occupying the left nasal cavity (> Fig. 20.13a). The mass encroached on and obstructed the left maxillary sinus, left anterior ethmoid air cells, and anterior left frontal sinus. There was no intracranial extension.

Options for Treatment

The mainstay of management for esthesioneuroblastoma is surgery followed by radiotherapy. The surgical resection should include a formal anterior ventral skull base resection with removal of the cribriform plate. Both open and endoscopic resections have been performed, depending on the extent of tumor and surgeon preference.

Treatment of the Primary Tumor

The patient was offered and underwent an extended endoscopic endonasal skull base approach with a modified subtotal Lothrop procedure to access and resect the anterior skull base tumor (> Fig. 20.13c–e). The mass was pedicled to the medial aspect of the superior and middle turbinates. There was no intracranial extension. The maxillary, ethmoid, frontal, and sphenoid sinuses were free of tumor. The ipsilateral cribriform, overlying dura, falk cerebri, and olfactory nerve were resected. Free margins along the entirety of the mass and middle turbinate were resected and were free of tumor. The pathology report revealed esthesioneuroblastoma, Hyams’ grade 2. The skull base defect was repaired with an ipsilateral pedicled nasoseptal flap harvested from the lower septum and nasal floor.

Adjuvant Treatment

The patient was referred to radiation oncology for adjuvant radiation therapy. She underwent a PET/CT at 8 weeks postoperatively, which revealed no evidence of metastatic disease. She was treated to the left nasal cavity region with IMRT treatment.

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planning. She received 6112 cGy in 34 fractions over 50 elapsed days. Early in treatment, she had no treatment-related complaints. Further into the treatment, she complained of nasal stuffiness, darkening of her skin; also, of white plaque on her tongue, which was treated for a fungal infection with fluconazole. Overall, she tolerated the treatment well. She did not require a treatment break. She lost about 10 lb during the course of the treatment.

Summary of Treatment
The patient was treated with complete surgical resection via an endoscopic endonasal ventral skull base approach for a Kadish stage A esthesioneuroblastoma. There was no evidence of metastatic disease. She received postoperative radiotherapy to the left nasal cavity. The patient is now 4 years postoperative with no evidence of recurrent disease.

References
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Reconstruction of the Anterior Skull Base

21 Reconstruction of the Anterior Skull Base
Anthony G. Del Signore, Zhong Zheng, Alfred Marc C. Iloreta Jr., Brett A. Miles, and Satish Govindaraj

21.1 Introduction
Neoplasms of the skull base are challenging to treat given the complex anatomy of the region and potential risk of major complications, such as cerebrospinal fluid (CSF) leaks, meningitis, and osteomyelitis. What was once addressed with open techniques, skull base surgery has progressed steadily and dramatically over the past decade with the advent of advanced expanded endoscopic techniques. Technological improvements, enhanced optical visualization, and miniaturization of instrumentation have allowed for more advanced lesions to be addressed endoscopically with minimal collateral morbidity, improved functional outcomes, and uncompromised oncologic results. Concordantly, resultant skull base defects after resections have also evolved, from smaller defects encountered in solely sellar pathology to larger sinonasal lesions with intradural and even intra-arachnoidal components. Closure of these defects has required a similar progressive evolution as the variety of lesions, sites, convexities, and reconstructive complexity has increased.

The reconstructive armamentarium available for the skull base surgeon has needed to match the variety of defects encountered. Initial experience with single or multilayered free tissue grafts was adequate for smaller skull base defects but proved to be insufficient for larger defects with increased complication rates. A multitude of reconstructive techniques and options have been reported beyond the currently available dural substitutes and nonvascularized free tissue grafts. Instead, current dogma utilizes a combination of both nonvascularized grafts and vascularized tissue pedicled locoregionally or via free tissue transfer. The advanced techniques allow for a robust repair of the larger skull base defects with acceptable complication rates. Regardless of the materials used or the complexity of defects encountered, the basic tenants remain the same: (1) obtain an initial watertight dural closure, (2) perform a multilayer closure, and (3) utilize vascularized tissue to obtain a stable barrier between the sinonasal and intracranial cavity.

Note
The tenets of a successful skull base reconstruction include obtaining a watertight dural closure, a multilayer closure, and the utilization of vascularized tissue to obtain a stable barrier between the sinonasal and intracranial cavity.

21.2 Relevant Anatomy
A detailed understanding of anterior skull base (ASB) anatomy is crucial to the successful reconstruction of the defects given the interplay of unique geometry, complex neurovascular structures, and multiple layers. The ASB is broken down into the anterior two-thirds and composed of the frontal and ethmoid bones and the posterior one-third formed by the planum sphenoidale.

More specifically, this area can be classified by the elected approach for a given lesion, that is, transcribriform, transplanum/tubercular, and transsellar. For a transcribriform approach, the cribriform plates are transgressed and the defect is limited laterally by the lamina papyracea/medial rectus, anteriorly by the frontal sinus/anterior ethmoidal artery, and posteriorly by the posterior ethmoidal arteries. The cribriform plates give rise to the midline crista galli, a vertical projection, which the falk cerebri attaches anteriorly. The olfactory bulbs are superior to the plate within the dura and olfactory filaments are transmitted through the foramina located within the fovea ethmoidalis to the underlying nasal mucosa.

Transplanum/transstubercular defects involve transgressing the planum sphenoidale or the roof of the sphenoid sinus. The area is composed of the tuberculum sellae posteriorly, anteriorly by the posterior ethmoidal arteries, and laterally by the optic nerves.

Transsellar defects involve an osteotomy of the sellar face with subsequent durotomy to gain access to pituitary lesions. Superiorly, the roof of the sella is formed by the diaphragm sella which consists of a dural extension from the dorsum sella to the tuberculum sella. The lateral boundary is the cavernous sinus, which houses the cavernous segment of the internal carotid artery, oculomotor nerve, trochlear nerve, ophthalmic division of the trigeminal nerve, abduens nerve, and the sympathetic plexus of the carotid.

21.3 Evaluation of Anterior Skull Base Defect and Determining Options for Reconstruction
Defect and patient factors are critical when evaluating reconstructive options available. Defect location on the skull base, size, rate of CSF flow, and degree of the arachnoid disruption are major considerations in repair success and should be evaluated critically. Secondly, patient comorbidities including raised intracranial pressure (ICP), prior surgical manipulation or radiation therapy exposure, and persistent pneumocephalus are pivotal in the success of skull base closure.

Note
Increased intracranial pressure, prior surgery, prior radiation therapy exposure, and persistent pneumocephalus adversely impact skull base reconstruction.

21.3.1 Location
The location of the skull base defect in relation to the origin of the supplying vessel plays an integral part in flap utilization, especially for pedicled local and regional vascular flaps. The design and extent of tissue harvested is dependent on the vascular supply and potential arch of rotation. For example, a
defect involving the ethmoid, planum, sella, or clivus may be easily reconstructed with the posteriorly based nasoseptal flap, while a primarily anterior defect, such as a high posterior frontal table, may be better suited with an anterior septal based flap or pericranial flap.

21.3.2 Size
Defects less than 1 cm, typically seen during CSF leak closure, can be reliably repaired (>90%) with the utilization of multilayered free grafts. For defects greater than 1 cm, from resection of benign or malignant sinonasal lesions, the utilization of vascularized flaps is an important adjunct.

21.3.3 Arachnoid Disruption and Ventricle Involvement
The resultant defect must also be evaluated to determine if there is disruption of arachnoid cisterns or third ventricular involvement, as these results in a high-flow CSF leak. The importance of a high-flow CSF leak is illustrated with the higher reconstruction failure rate of 6% compared to low-flow states (2%). In addition to the use of a multiple-layered closure utilizing vascularized tissue, temporary diversion of CSF via a lumbar drain may be considered. Although significant controversy exists on the topic, a review of the literature has shown compelling evidence that CSF diversion may not be needed in this patient population. Furthermore, judicious use of lumbar drains is advocated, as the literature suggests a 3% risk of major complications and a 5% risk of minor complications with the use of lumbar drains.

21.3.4 Raised Intracranial Pressures
Elevated intracranial pressures encountered in the perioperative or postoperative period can lead to reconstruction failures, such as in obese patients, patients with subarachnoid hemorrhage, or cerebral edema from lesion excision and manipulation. The need for either an external ventricular drain or cerebral shunt should be considered along with the use of acetazolamide to help decrease CSF production.

21.4 Classification of Skull Base Defects
The complexity and diversity of the skull base region and associated reconstructive factors have not allowed for a single classification system to be devised. Several authors have attempted to categorize defects based on anatomical confines, associated pathologies, and reconstructive requirements. Initially, authors attempted to divide the skull base into anterior, middle, and posterior areas corresponding to anterior, middle, and posterior cranial fossa. Irish et al reviewed a cohort of 77 patients and divided the skull base into three zones (I, II, III) based on anatomical boundaries, tumor growth patterns within the different zones, and help to define surgical corridors (Fig. 21.1). Nameki et al utilized a four-stage system to describe defects according to size in the context of open approaches.

21.5 Reconstruction: General Principles
21.5.1 Site Preparation
Prior to any formal reconstruction, the area should be thoroughly surveyed. Although a reconstructive plan should be detailed prior to surgical manipulation, surgical margins may extend further or deeper than initially anticipated. Initial survey determines exposure to carry out the necessary reconstruction. The need for working space is important for the delivery of the reconstructive option to the defect site. Often the surgical corridor selected for tumor removal provides this access but in cases when a regional pedicled flap or free flap is utilized, there may be a need for supplemental incisions or a tunnel to be performed.

The importance of assessing subsite involvement and defect extent cannot be overstated. For instance, a defect that spans the sella to the frontal sinus may need a different reconstructive plan than solely a sellar or ethmoid defect. Also, determining...
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Fig. 21.1 Irish classification\textsuperscript{16} which divides the skull base into three regions. Zone I tumors originate in the anterior skull base. Zone II involves the lateral skull base with extension into the infratemporal fossa and pterygopalatine fossa. Zone III starts laterally from the ear, parotid, or temporal bone and extends to involve the posterior cranial fossa.

Fig. 21.2 Yano classification\textsuperscript{18} of skull base defects.
the collateral damage from tumor extirpation is important, as it can restrict reconstructive options. For example, an initial plan to use a nasoseptal flap reconstruction can be altered if there is septal tumor involvement found intraoperatively or if the sphenopalatine artery was ligated.

Another important factor of defect assessment is to determine the extent of bony ledges remaining. The reconstruction of these complex defects often involves an underlay and overlay multilayered closure and is ideally supported by an intact bony ledge. This is exemplified when a unilateral resection of the ethmoid roof is performed in an attempt to preserve olfaction with the contralateral olfactory bulb. In this case, the resection is often taken flush with the crista galli, and no horizontal ledge is available for flap placement, leaving the flap to run in a vertical configuration along the crista galli. This change in orientation from a horizontal to vertical construct increases the complexity of the reconstruction and raises the risk of CSF leak postoperatively.

There are several important points to consider in the exposure and site preparation. First, a complete sphenoidectomy with meticulous removal of bony ledges and septations is essential. Overlying mucosa of the surrounding defect site is removed, but literature has shown that it does not need to be comprehensive as there is no evidence of increased mucocoele formation from trapped mucosa. Instead, maintenance of adjacent mucosa with native blood supply and minimizing mucosal trauma or excessive cauterization can expedite mucosal integration of the reconstruction site. A Draf III frontal sinusotomy may sometimes be needed if the reconstruction is taken to areas anterior to the anterior ethmoidal artery. These modifications can help with flap placement, ensure postoperative frontal sinus function, and assist with in-office endoscopic tumor surveillance.

**21.5.2 Graft Healing**

Graft healing is dependent on the source material utilized. Free tissue grafts depend on adherence to underlying and overlying tissues with fibrin bonds and serum imbibition occurring for the first several days. Any factor that leads to a separation of that initial attachment, such as hematoma, seroma, CSF leak, or foreign body, will prevent revascularization and can result in a CSF fistula. The initial bonds allow inosculation followed by revascularization and neovascularization to occur. Revascularization is critical as it allows for the survival of the graft, remodeling, and remucosalization of the defect. The use of alternative constructs, that is, acellular dermis, allows for secondary intention, granulation tissue formation, and eventual reepithelialization. In vascularized tissue flaps, the primary blood supply allows for perfusion of the defect site and accelerated phases of wound healing, as it does not solely depend on vascular ingrowth from the recipient bed. If a CSF leak is identified in the postoperative period, early exploration is warranted, as fistula tract formation may not close with conservative measures.

**21.5.3 Bolstering Repairs**

For all endoscopic-assisted reconstructions, bolstering the repair provides support during the initial healing phases especially in high-flow CSF defects. The finalized mucosal repair is often set into place with a perimeter of Surgicel (Ethicon US, LLC, Somerville, New Jersey), this initial layer allows the inflammatory cascade to initiate at the periphery and “sets” the flap in place (Fig. 21.3a). To prevent graft migration and ensure flap apposition with the underlying bony defect, firm Nasopore (Polyganics, Groningen, the Netherlands) of dissolvable packing can be bolstered in strategic areas. Tissue sealant such as DuraSeal (Confluent Surgical Inc, Waltham, Massachusetts) is placed not to act as a dural seal but as a three-dimensional pack (Fig. 21.3b). This is then followed by another layer of dissolvable nasal packing, which not only applies further pressure during initial stages of healing, but also prevents migration of the reconstruction upon removal of nondissolvable packing when used. Finally, nonabsorbable packing, when used, is placed to bolster the entire reconstructive complex. The choice of nonabsorbable packing depends on the location of the defect and the necessary force required to bolster reconstructions (Fig. 21.3c). For defects that require more radial force, typically sellar and clival defects, a 12-F Foley catheter filled with saline is an excellent option to provide gentle pressure (Fig. 21.3d). For defects that involve the ethmoidal skull base or planum sphenoidale require bolstering from below, nonabsorbable expandable packing is an excellent option. The duration of nonabsorbable packing is dictated by the complexity of the repair and dependent on the aforementioned risk factors for CSF leak and is typically left in place for 3 to 7 days.

**21.6 Reconstructive Options**

Techniques in repairing skull base defects after extended endonasal resection continues to evolve and expand. Although there is not a codified algorithm, the available options can be considered a stepwise reconstructive ladder. Autologous tissue grafts are available in the forms of bone, fascia, fat, cartilage, muscle, and mucosa, both free and pedicled. Nonautologous manufactured matrices can be used but at an added cost. Ultimately, the
utilization of a specific closure material and reconstructive technique is dictated by defect factors, surgeon familiarity, and experience. ▶ Table 21.1(a,b) provides a summary of the grafts with their harvest location, pedicle type, and special considerations to bear in mind. The remainder of the text discusses the various reconstructive options available.

<table>
<thead>
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<th>Note</th>
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<tr>
<td>The utilization of a specific closure material (autologous vs. nonautologous) and reconstructive technique is dictated by defect factors, surgeon familiarity, and experience.</td>
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### 21.6.1 Reconstruction of Foveocranial Defects

Foveocranial defects can be median or paramedian involving the ethmoid bone or the posterior table of the frontal bone. Defects often spare the anterior table of the frontal bone and the orbit laterally. They are usually lower-volume defects amenable to endoscopic repair with free grafts or vascularized locoregional pedicled flaps. The reconstructive goals of foveocranial defects include a watertight dural closure to ensure a separation of intracranial contents from sinonasal cavity and obliteration of dead space. Frontal buttress and superior orbital rim are intact in foveocranial defects, therefore, bony recon-
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Table 21.1 Reconstructive options for skull base defects

<table>
<thead>
<tr>
<th>Graft type</th>
<th>Pedicle</th>
<th>Special considerations</th>
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<tbody>
<tr>
<td><strong>a. Nonvascularized grafts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acellular grafts (i.e., Alloderm, Duragen)</td>
<td>-</td>
<td>Commercially available. No donor site morbidity</td>
</tr>
<tr>
<td>Mucoperichondrium/mucoperiosteum</td>
<td>-</td>
<td>Harvested from middle turbinate if resected. Other donor sites include septum, nasal floor, or side wall</td>
</tr>
<tr>
<td>Fat</td>
<td>-</td>
<td>Harvested from abdomen with minimal donor site morbidities. Ability to contour to defect. Use as “plug” technique</td>
</tr>
<tr>
<td>Tensor fascia lata</td>
<td>-</td>
<td>Harvested from lateral thigh with minimal donor site morbidities. Use as a “gasket seal” or double-layer “button graft” technique</td>
</tr>
<tr>
<td>Fat</td>
<td>-</td>
<td>Harvested from abdomen with minimal donor site morbidities. Ability to contour to defect. Use as “plug” technique</td>
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**Note:** Nonvascularized grafts are best suited for small defects with low CSF flow and in nonirradiated patients.

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The reconstructive goals of foveocranial defects include a watertight dural closure to ensure a separation of intracranial contents from sinonasal cavity and obliteration of dead space.

Note

The data strongly support superior outcomes using vascularized tissue for skull base reconstruction especially in patients with a previous radiation history or planned adjuvant radiotherapy.

Nonvascularized Tissue

Acellular Grafts and Collagen Matrix

Nonvascularized tissue can be utilized alone or in combination with vascularized tissue for reconstruction. Acellular grafts in the form of acellular human dermis (Alloderm, LifeCell Corporation, Branchburg, New Jersey) has gained popularity for resurfacing anterior cranial fossa defects for reconstructing a sealed flap, and temporoparietal fascia flap. Alternatively, free tissue transfer is also an option when locoregional flaps are unavailable, such as the pliable radial forearm fasciocutaneous free flap.
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barrier. The material has the advantages of saving operative time for graft harvest and reconstituting in normal saline within 10 minutes. Contrary to free mucosal grafts, the graft material tends not to shrink during healing, minimizing the possibility of reconstruction failure.

There are also a multitude of manufactured collagen-based dural replacements available for dural repair. These products are matrices of treated animal collagen that have been processed to remove cellular and antigenic components and treated to induce cross-linking and incorporation with native dural margins. These provide an optimal scaffold and environment for fibroblast infiltration which occurs by 4 weeks, collagen formation occurs by 8 weeks, and dural incorporation completed by 16 weeks.21,22

Patient Selection

Skull base reconstruction using nonvascularized grafts alone, both acellular dermis and manufactured collagen, is ideal for patients with small defects with little to no CSF egress. Larger defects should be bolstered with a multilayered reconstruction with the possible use of vascularized tissue. Little data exist supporting one material over another. Although, the healing of graft material has been examined, and data show a more rapid mucosalization and quicker resolution of crusting with the engineered collagen products over acellular human dermis.23

The choice of material is typically dependent on surgeon preference, cost, and availability, in particular, healthcare institutions.

Note

Large skull base defects should be bolstered with a multilayered reconstruction with vascularized tissue.

Surgical Technique and Considerations

Acellular dermis or collagen matrices can be used in a multilayered closure or as a single-layered technique. When used as an underlay, the purpose is to create a watertight seal and serve as the direct subdural (between brain and dura) or epidural (between dura and osseous skull base) repair. The material is often shaped larger than the defect (approximately 5–10 mm beyond the dural margin in all directions) so there is adequate material under the bony ledges and apposition with the remaining dural margin (▶ Fig. 21.4a). Upon proper placement of the inlay graft, there should be adequate transmission of the CSF pulsations without evidence of CSF egress (▶ Fig. 21.4b). In the case of acellular dermis being used as an overlay, if defect geometry or size prevents inlay or dural substitute is used as an inlay, then the graft can be placed over the demucosalized bone.

Perioperative Management

Perioperative considerations include the need for meticulous sinonasal hygiene with nasal saline irrigations, minimizing crusting of sinonasal cavity, and mitigating the risk of poor wound healing.

Pearls

● Small (< 1 cm) or sellar defects can be prime candidates.
● Low to no flow CSF leaks, one may use this material solely for reconstruction. For complex defects and high-flow leaks, it is used as the primary layer.
● The initial layer is placed as an underlay to provide an initial watertight seal.

Fig. 21.4 (a) Acellular collagen matrix laying over the skull base defect and is sized 5 to 10 mm beyond all edges. (b) Acellular collagen matrix in an inlay of the defect creating a watertight seal to prevent CSF egress.
Reconstruction of the Anterior Skull Base

Cellular Grafts (Mucoperichondrium, Mucoperiosteum, Fat, Dermal Fat, Fascia, Bone, Cartilage)

Since the initial endoscopic repair of a CSF leak utilizing free tissue grafts as described by Wigand,24 various tissue types have been utilized as donor source for dural closure. The advantages of free grafts include readily available material from both local and distal sites, relative ease and expeditious time of harvesting, minimal to no donor site morbidity, versatility to tailor to unique defect sizes or contours, and placement of grafts with minimal tension. Autologous free grafts avoid foreign body reactions and allow primary healing with the surrounding mucosa even when placed overlying bone, despite lacking an axial blood supply.25 On the other hand, the absence of a vascular pedicle may cause the donor tissue resorption and contraction during the healing, which should be carefully considered to prevent the development of a delayed leak.

Intranasal free grafts can utilize mucoperichondrium and mucoperiosteum, in the form of septal flaps, turbinate flaps, and nasal floor flaps. Flaps from these sites can be harvested with relative ease utilizing either cold steel or needle tip cauterization. When septal mucosa is harvested, the resultant bare cartilaginous or boney defect may take several weeks to months to completely remucosalize,26 which may increase the risk of septal perforation and prevent utilization of a pedicled vascularized nasoseptal flap in the future.

Mucosal grafts can also be harvested from the middle or inferior turbinates and nasal floor, with the latter providing a large area of thick mucosal tissue if extended to the nasal floor or lateral wall. The harvesting of middle turbinate flap on an intact turbinate can be technically challenging and carries an increased risk of CSF leak at the superior attachment of the middle turbinate along the skull base. To minimize this risk, if middle turbinectomy is performed to facilitate adequate exposure and working room during the initial approach, free mucosal grafts can be harvested extracorporeally. Nasal floor mucosal grafts are an option that causes minimal donor site morbidity and has virtually no risk of bleeding since there is no arterial pedicle that directly supplies this area as in the turbinates.

Abdominal fat grafts have also been reported for skull base reconstruction. A “bath plug” technique has been described, whereby a fat graft is placed through the skull base defect spanning both the intranasal and intracranial cavities and held in place by the ambient CSF pressure.27 Furthermore, the fat graft allows for a three-dimensional scaffolding to obliterate dead space in concave defects. Recent modifications have included a dermal layer to the fat graft. Although a separate donor incision and sterile instrumentation/preparation are required, the harvest does not significantly prolong operative time.

Tensor fascia lata harvested from the lateral thigh is used extensively in dural reconstruction as both an inlay and onlay technique. The “gasket seal” modification utilizes a fascia lata onlay with rigid construct of bone or Medpor to be countersunk and wedged into the defect.28 This technique provides a watertight dural seal that can be used alone but is often combined with a vascularized pedicled flap. In addition, the use of a double fascial layer graft termed as the “button graft” has also been described.29 Two layers of fascia layers are sutured together to allow movement as a single unit and accurate deployment, minimizing the risk of graft migration and combines both an inlay and overlay reconstruction.

Patient Selection

Avascular cellular reconstructive techniques can be utilized as the sole reconstructive layer in smaller defects or in conjunction with a vascularized nasal septal flap for larger defects.

Surgical Technique and Considerations

Free Mucosal Grafts

- Careful intraoperative examination is required to ensure the intended donor site is free of disease, especially in patients with sinonasal malignancies, given the risk of field change and dysplasia.
- Measuring the defect size allows for adequate graft design while keeping the donor site morbidity low.
- Utilizing a curved Beaver blade or ophthalmic crescent knife for the initial incision facilitates elevation of the flap off the underlying cartilage or bone.
- Marking the mucosal surface of the graft with a marking pen prevents inadvertent reversed placement, mitigating postoperative mucocele formation.
- The donor site can remucosalize without intervention, a Doyle or Silastic splint may be used to cover the septal donor site defect, minimizing crusting and maintaining moisture in the early postoperative period.

Abdominal Fat Grafts

- Depending on the volume of fat needed, donor sites can be harvested from the ear lobe, abdomen, or thigh if concomitant tensor fascia lata harvest is used for reconstruction.
- Fat volume can be estimated with a pituitary curette measuring the defect dimensions and depth.
- Meticulous hemostasis and gentle tissue handling at the donor site help to prevent hematoma or seroma formation. Judicious use of cautery with electrocautery should be employed to prevent atrophy of fat.
Tensor Fascia Lata Graft

- Tensor fascia lata grafts are versatile and can be tailored to the size and contour of the skull base defect.
- Limits of dissection marked prior to incision on the lateral thigh (Fig. 21.5a).
- The boundaries include laterally 4 cm anterior to lateral intermuscular septum, inferiorly 10 cm superior to lateral femoral condyle joint, and superiorly 15 cm from anterior superior iliac spine. Typically, a graft size up to 20 × 10 cm can be harvested.
- Meticulous hemostasis and compression dressings help prevent postoperative hematoma or seroma.
- The defect size is measured, and the fascia lata is prepared by oversizing the defect circumferentially by 20 mm. To ensure a watertight dural closure, the underlay fascia graft should overlap normal dura or boney ledge by 5 to 10 mm circumferentially. An overlay graft can be used to bolster the reconstruction, which is measured to extend beyond the boney defect and placed over the denuded bone circumferentially.

Modifications Utilizing Tensor Fascia Lata

- “Gasket seal”
  - An overlay of tensor fascia lata that is 20% larger than the final defect is prepared to ensure complete coverage.
  - A rigid construct can be fashioned from septal bone, vomer, or a Medpor implant to approximate the area of the defect, allowing it to countersink and wedge into the defect creating a watertight seal (Fig. 21.5b).
  - The fascia–rigid construct complex can either be covered with DuraSeal or vascularized tissue.
- “Bilayer button grafts”
  - An inlay–onlay construct is created by suturing together two layers of fascia. The inlay portion is fashioned 25 to 30% larger than the defect, to allow adequate inset, and the onlay portion is 5 to 10% larger than the defect for apposition against the dura. The two pieces are sutured together with two to four, 4–0 Nurolon sutures (Ethicon, Bridgewater, New Jersey).
  - The bilayer construct is then inserted in the subdural and epidural spaces as a “button” to minimize graft migration and create a watertight dural seal (Fig. 21.5c).

Fig. 21.5 Utilization of tensor fascia lata (TFL) graft. (a) Markings for TFL harvest. A line is drawn from the femoral condyle to the anterior superior iliac spine. The line is then “cut” in one-half and in one-third. The incision spans the one-half mark and the distal one-third mark, approximately 4 cm from the lateral intermuscular septum. (b) Gasket seal: overlay of TFL (outlined in blue) with the Medpor implant (outlined in black) countersunk and wedged into the defect. (c) “Bilayer button graft”: inlay–onlay construct within defect (original defect—black outline, onlay: 5–10% larger than defect—blue outline, inlay: 20–30% larger than defect—yellow outline). (d) The unilayer construct (A) and bilateral (B) is inserted in the subdural and epidural spaces to create a watertight dural seal.
The vascular pedicle is approximated submucosally along the

● Given the close proximity of the nasal mucosa to the sinonasal lesion, the NSF is often raised prior to resection. In cases where tumor burden involves septal mucosa, alternative modalities should be considered.

● The vascular pedicle is approximated submucosally along the anterior face of the sphenoid sinus, inferior to the sphenoid sinus natural ostium, and above the arch of the posterior choana.

Vascularized Tissues
Nasoseptal Flaps

First introduced in 2006, the vascularized pedicled nasoseptal flap (NSF) or Hadad-Bassagasteguy flap is often the first reconstructive choice for most endoscopic skull base surgeons. The flap utilizes the mucoperichondrium/mucoperiosteum of the septum pedicled posteriorly on the posterior septal artery, a terminal branch of the internal maxillary artery, acting as the arc of rotation. The NSF has the versatility to incorporate a large area of nasal cavity mucosa and tailor flap design to the resultant defect size, allowing it to be used for a multitude of ventral cranial base defects. Utilization of the NSF for endoscopic reconstruction of high-flow CSF leak defects have been reported to have a 5% postoperative leak rate, comparable to that of open techniques, lending to wider acceptance for endoscopic resection and reconstruction when possible.\(^3\)

Patient Selection

The large size of potential tissue harvest allows it to span from orbit to orbit and from lower clivus to frontal sinus. Typically, two adjacent subites, cribiform and planum or sella and clivus, may be covered by the flap length. In the case of a suprasellar and infrasellar defect, there may not be adequate tissue to address at the same time. The location of tissue harvest is dependent on multiple patient and tumor factors: nasal cavity size, septal deviation, septal perforation, prior sinus surgery, laterality of tumor, involvement of septal mucosa, and location of resultant defect. Preoperative imaging can be used to estimate the dimensions of the flap and the defect to estimate the size of the flap to be harvested.

Note

Choosing a donor site for soft tissue skull base reconstruction is dependent on multiple patient and tumor factors: nasal cavity size, septal deviation, septal perforation, prior sinus surgery, laterality of tumor, involvement of septal mucosa, and location of resultant defect.

Surgical Technique and Considerations

- Using a needle tip monopolar electrocautery mucosal incisions are made (Fig. 21.6a). A vertical incision then connects superior and inferior incisions, commonly carried out to the head of the inferior turbinate.
- It is essential to completely perform all mucosal cuts prior to elevation, with particular attention to the face of the sphenoid, rostrum, and decussating fibers along the floor of the septum to ease elevation of the flap.
- Once elevation is completely off the sphenoid face, the flap is stored in the nasopharynx or ipsilateral maxillary sinus until it is needed for the reconstructive portion (Fig. 21.6b).

Perioperative Management

Bolstering the repair with either a Foley balloon catheter or nondissolvable nasal packing is usually left in place for 3 to 7 days depending on the intensity of the CSF leak. Postoperative imaging may help to assess the adequacy of the reconstruction, evaluating for hemorrhage, possibility of flap migration, flap viability, and presence of dead space. If the postoperative magnetic resonance imaging (MRI) shows a lack of contrast enhancement, early exploration may be needed to assess flap viability. In certain cases, relieving the pressure placed by packing material may ensure flap survival. Patients are started on nasal saline sprays for the first week postoperatively and then transitioned to nasal saline irrigations to mitigate crusting and reestablish proper sinonasal function.

Pearls

- Alignment of the mucoperichondrial/peristeal surface directly against the dura and bone defect should be assured to prevent flap migration, contracture of the flap, and mucocele formation (Fig. 21.6c).
- As with any other vascular pedicle, it should be protected while drilling the face and floor of the sphenoid and when utilizing the microdebrider.
- Judicious use of the electrocautery should be practiced during the initial mucosal cuts over the face of the sphenoid and arch of the choana to prevent inadvertent thermoinjury to the vascular pedicle.
- Modifying the inferior and anterior mucosal incisions allows lengthening and widening the mucosal flap design to extend the reach to the frontal sinus, lower clivus, and complete coverage of the ethmoid skull base.
- A free mucosal graft (obtained from the resected middle turbinate) placed over the exposed septal cartilage can accelerate mucosalization of the donor site.

Pericranial Flaps

The pericranial flap (PCF) has been extensively used in reconstruction after open craniofacial resections. With the advent of endoscopic techniques, it has been adapted for defects after extended endonasal or endoscopic-assisted open resections. Its advantages include a reliable vascular supply, large size, and often outside of the field of previous irradiation. It is ideal for reconstruction when the nasoseptal flap is otherwise unavailable. The vascular supply is derived from the deep branches of the supraorbital and supratrochlear arteries.
Reconstruction of the Anterior Skull Base

Fig. 21.6 Utilization of the nasoseptal flap (NSF). (a) Incisions of the NSF as noted by the dotted yellow line. The sphenoid os is used as a reference with the first cut made approximately 2 cm from the skull base in an attempt to preserve olfaction. The second cut is taken over the face of the sphenoid and inferiorly along the posterior septum to the floor of the nasal cavity. The red line denotes the posterior septal artery, the main pedicle of the reconstructive flap. (b) The nasoseptal flap harvested and reflected laterally and placed into the maxillary sinus for safe keeping. It is important to get excellent lateral extension so as to allow the flap to be rotated appropriately. (c) Nasoseptal flap rotated and placed over the skull base defect.

Note
The pericranial flap offers reliable vascular supply, large size, long pedicle length, and often outside of the field of previous therapy.

Traditionally, the PCF is harvested through a bicoronal incision in conjunction with open craniofacial resection. Recently, endoscopic harvest technique has significantly reduced donor site morbidity. When combined with a nasionectomy, the PCF can be transposed endonasally to reconstruct defects of the anterior fossa, posterior sella, and clivus. The PCF can also be combined with the NSF.

Patient Selection
The PCF is a critically important reconstructive option in patients with compromised vascular supply to the NSF.

Surgical Technique and Considerations
- Endoscopic-assisted elevation of the pericranial flap allows for minimal donor site morbidity (Fig. 21.7a).
- Doppler can help identify supraorbital and supratrochlear arteries at the supraorbital notch, and a 3-cm width can be marked centered at the vascular pedicle. A 2-cm midline and two 1-cm lateral port incisions are carried down through the galea, placed at the hairline (Fig. 21.7b).
Subgaleal elevation is performed under direct endoscopic visualization until supraorbital rim and neurovascular bundle are identified. Posterior subgaleal dissection can also be performed to maximize flap length (Fig. 21.7c). If the pedicle traverses supraorbital foramen instead of notch, osteotomes can be used to increase arc of flap rotation (Fig. 21.7d).

To transpose the PCF endonasally, a glabellar incision and nasionectomy can be used (Fig. 21.7e).

It is important to perform a Draf III frontal sinusotomy to allow delivery of the PCF and held in place with intranasal packing (Fig. 21.7f).

Perioperative Management
Placement of a suction drain can be used but compressive head dressing should be avoided to prevent vascular compromise.

Pearls
- The size, vascularity, and durability of the PCF make it ideal for reconstruction in patients requiring postoperative radiotherapy with low rate of late complications or failures.
- Endoscopic harvest allows for minimal donor site morbidity.
- Intraoperative Doppler ultrasound can help map the vascular pedicle thereby mitigating injury.

Temporoparietal Fascia Flap
The temporoparietal fascial flap (TPFF) can be harvested to cover a rather large area, up to $17 \times 14 \text{ cm}$. The TPFF is a pliable flap axially based on the anterior or frontal branch of the superficial temporal artery. The laterally based pedicle allows for reconstruction of a variety of skull base defects, including sellar, parasellar, clival, nasopharyngeal defects.
Reconstruction of the Anterior Skull Base

Patient Selection
Preoperatively, it is imperative to determine the viability of the superficial temporal artery with Doppler ultrasound, especially in patient with prior coronal incisions.

Surgical Technique and Considerations
- **●** The bifurcation of superficial temporal artery occurs within 0.5 to 2 cm of tragus in 90% of cases and above the zygomatic arch in 60 to 88% of cases.
- **●** A hemicoronal incision ipsilateral to the defect is performed, and subdermal dissection at the level of hair follicles is carried out (Fig. 21.8a).
- **●** The TPFF is continuous with galea aponeurotica superior to the temporal line and can be elevated off the superficial layer of the deep temporal fascia down to the zygoma, preserving a pedicle width of 2 cm to prevent torsion (Fig. 21.8b).
- **●** Endoscopic-assisted TPFF harvest has also been reported.
- **●** The frontal branch of the facial nerve crosses the zygoma obliquely just deep to the temporoparietal fascia. To prevent facial nerve injury, dissection should be kept posterior to a line drawn from tragus to lateral canthus. Transposition of harvested TPFF is tunneled through the infratemporal fossa to the pterygopalatine fossa (PPF). Wide maxillary antrostomy is performed and identification of key neurovascular structures of the PPF, pterygoid plates are exposed and drilled down to make room for the TPFF.

Perioperative Management
A head dressing should be used judiciously, with care to prevent pedicle compression. A Jackson Pratt drain can be used alternatively.

Pearls
- **●** The communication channel between the infratemporal fossa and the pterygopalatine fossa should be enlarged to ensure proper transmission of the vascular pedicle.
- **●** A percutaneous tracheostomy dilation cannula can assist in sequentially dilating this tract prior to flap and pedicle transfer.

**Note**
When planning a temporoparietal fascial flap, preoperatively, it is imperative to determine the viability of the superficial temporal artery with Doppler ultrasound.

**Fig. 21.8** Utilization of the temporoparietal fascia flap. (a) Hemicoronal incision ipsilateral to defect (dotted line). Care must be taken as to not injure the superficial temporal artery which courses below. (b) Design of TPFF (shaded) with its rotational axis at the base allowing for the transposition and tunneling of the flap into the pterygopalatine fissure. (c) The posterior bony wall of the maxilla and later pterygoid plate (LPP) can be resected (A) to tunnel the temporoparietal flap under the zygoma (B).
Free Flaps

Radial Forearm Fasciocutaneous Free Flap

Patients with prior irradiation and/or large complex defects may require microvascular free tissue transfer. Radial forearm fasciocutaneous free flap (RFFF) remains an excellent option when the defect volume is relatively small but obliteration of dead space or resurfacing of cutaneous defect is required. Its advantages include long pedicle length, pliability, thin profile, and reliable vascular supply. Its disadvantages include donor site cosmesis and sensory disturbances at the donor site. An additional disadvantage is the presence of hair-bearing skin which is not ideal. The flap can be harvested as a fascia flap only if this is a concern.37,38,39,40,41,42,43

Patient Selection

The RFFF is well suited for small-volume defects when locoregional flaps are not available or inadequate.

Note

RFFF is an excellent option for skull base reconstruction when the defect volume is relatively small but obliteration of dead space or resurfacing of cutaneous defect is required.

Surgical Technique and Considerations

- The RFFF pedicle can be found in the lateral intermuscular septum between the flexor carpi radialis and brachioradialis muscles.
- A positive preoperative Allen’s test verifies patency of the ulnar artery and anastomosis of the superficial and deep palmar arches to prevent distal extremity ischemia after harvest.
- During flap elevation, the paratenon connective tissue over flexor muscle tendons should be preserved to facilitate skin graft healing.
- Microvascular reanastomosis can be performed to superficial temporal artery or facial artery, and vein grafts are rarely needed to extend pedicle length (Fig. 21.9).
- If bony reconstruction is required, a radial forearm osteocutaneous flap may be harvested to include up to 40% of the circumference of the radius. The risk of fracture can be mitigated with distal radius fixation.44

Perioperative Management

A postoperative volar splint helps to prevent shearing force of underlying flexor tendons to improve skin graft adherence. A split-thickness skin graft is usually required to resurface donor site. Arm elevation helps to minimize postoperative edema.

Pearls

- Previous intravenous or arterial line placement can affect vascularity of the flap and should be considered if the line was placed less than 48 hours prior to harvest.
- Allen’s test can assess the continuity of the palmar arch and presence of any vascular insufficiency.
- Harvest of the nondominant donor arm will improve early and late functional outcomes.

21.6.2 Reconstruction of Parasagittal Orbitocranial Defects

Parasagittal orbitocranial defects involve a variable portion of the orbital laterally, with or without orbital exenteration. Orbitocranial reconstruction is a challenge dictated by the types of tissue that are resected, including dura, skin, bone, or globe. If a significant portion of the superior orbital wall is sacrificed, bony reconstruction in addition to soft tissue replacement may
be required to prevent brain herniation and pulsatile exophthalmos. Previous studies have described multilayered reconstruction with titanium mesh and split calvarial bone graft wrapped with a pericranial flap.45,46,47

Reconstruction after orbital exenteration deserves special consideration and maintaining a closed versus open cavity is a controversial decision. Advantages of open cavity include possibility ocular prosthesis; however, contracture of the cavity can lead to significant upper and midface deformities, especially with planned adjuvant radiation. Some authors argue for a closed cavity with a superior and more natural aesthetic appearance.47

Chepeha et al presented an orbital exenteration defect-oriented reconstructive schema assisting in reconstructive method selection. Type I defects involve orbital exenteration without disruption of the bony rim; type II defects include removal of less than 30% of bony orbital rim; and type III defects involve greater than 30% of bony orbital rim, in addition to the bony malar eminence and cutaneous defects.48 Reconstructive options include RFFF (▶ Fig. 21.10), anterolateral thigh (ALT), rectus abdominis, or chimeric scapular free tissue transfers.

Free Flaps

Anterolateral Thigh Fasciocutaneous Free Flap

Reconstruction of large composite skull base defects is important to obliterate dead space, separate intracranial contents from the sinonasal cavity, and to prevent CSF leaks, pneumocephalus, and ascending meningitis.

Since its introduction in 1984, the ALT free flap has increased in its popularity in skull base reconstruction, secondary to its large tissue bulk and minimal donor-site morbidities and reliable vascular pedicle. Another advantage is the ability to perform simultaneous ablative resection and flap harvest, with multiple cutaneous paddles available for resurfacing nasal, palatal, or orbital defects. The primary disadvantage of the ALT is the lack of bone for osseous reconstruction, although chimeric harvest of the femur has been reported.40,49,50,51

Note

The goals of reconstruction of large composite skull base defects is to obliterate dead space, separate intracranial contents from the sinonasal cavity, and to prevent CSF leaks.

Patient Selection

The majority of patients will have two to three sufficient cutaneous perforators if cutaneous reconstruction is required. Few patients are poor candidates for ALT harvest, with obesity and the resulting soft tissue bulk being the primary consideration if smaller defect reconstruction is required. The donor site is extremely well tolerated (▶ Fig. 21.11a–e).

Surgical Technique and Considerations

- The ALT flap is based on perforating vessels from the descending branch of the lateral circumflex femoral artery, which travels between rectus femoris and vastus lateralis muscles.
- Cutaneous perforators can be found within a region 2 cm lateral to and 2 cm inferior to the midpoint of a line joining anterior superior iliac spine and superolateral border of the patella.
- Preoperative Doppler can help identify location of cutaneous perforators.
- Skin paddles can be designed as large as 20 × 26 cm, and a pedicle length up to 16 cm can be obtained.
- Primary closure can be accomplished with undermining and with skin paddle up to 8 cm in width.
- Contraindications for the use of ALT free flap may include history of significant peripheral vascular disease and/or major lower extremity bypass surgery. In addition, a patient’s body habitus may preclude the use of an ALT due to excessive bulkiness as mentioned previously.52

Perioperative Management

Suction drain in donor site may be beneficial in preventing hematoma or seroma. Early ambulation and physiotherapy are recommended and can decrease postoperative morbidities.
Pearls

- The ALT has a variety of soft tissue options available, including muscle, fascia, fat, and skin with an extremely reliable vascular pedicle.

- Donor site morbidity is low and the flap is well tolerated by the majority of patients.

- Obese patients who require cutaneous reconstruction may have excessive bulk precluding the use of this flap.
Reconstruction of the Anterior Skull Base

Rectus Abdominis Musculocutaneous Free Flap

Patient Selection

The rectus abdominis musculocutaneous (RAM) free flap has been traditionally used for large complex orbitomaxillocranial defects.44 The large tissue volume and readily available skin paddle is ideally suited for reenforcement of duraplasty, obliteration of the sinonasal cavity, reconstruction of palate, and restoration of cutaneous defects and soft tissue contour. The RAM flap can also be combined with nonvascularized bone grafts for reconstruction of the orbital floor.53 The harvest technique can be altered to allow for an extremely long vascular pedicle if indicated, which is an advantage of this donor site.

Surgical Technique and Considerations

- The RAM flap is supplied by deep inferior epigastric artery and vein from the external iliac vessels. The vascular pedicle is found on the deep surface of the rectus muscle, and musculocutaneous perforators are found in the paraumbilical region.
- The anterior rectus sheath is preserved below the arcuate line to prevent postoperative hernias.
- Patients with central obesity are not ideal candidates due to excessive bulkiness.
- Recently, a modified approach has been described harvesting adipose tissue with only a small cuff of rectus muscle.54,55

Perioperative Management

Postoperatively, patients should be monitored for the resolution of ileus that may result with manipulation of the peritoneum.

Pearls

- Excellent vascular pedicle with large volume of soft tissue available for reconstruction.
- Donor site morbidity is less well tolerated, and may lead to postoperative delayed ambulation and impaired pulmonary clearance due to pain.
- This flap should be avoided in patients with significant abdominal surgery history (i.e., hernia repair or laparotomy).

Thoracodorsal Artery Scapular Tip Osteocutaneous Free Flap

Large orbitocranial defects often require bony reconstruction as well as soft tissue replacement to achieve the best results. Large superior orbital roof defects necessitate bony coverage to prevent pulsatile exophthalmos. In addition, special considerations should be given to reconstruct large orbital or midface defects with bone-containing free tissue transfers.48,56,57 In situations where adjuvant radiation is expected, significant defects may need osseous support to prevent retraction and graft shrinkage postoperatively. The scapular tip osteocutaneous free flap based on thoracodorsal artery system is an excellent option due to its long pedicle length and the availability of soft tissue and bony components that are independently mobile and capable of resurfacing complex three-dimensional composite defects.56,57

Note

The scapular tip osteocutaneous free flap is an excellent option for bony skull base reconstruction due to its long pedicle length and versatility in coverage of complex three-dimensional defects with the availability of multiple tissues types.

Patient Selection

Excellent aesthetic results and success in creating a closed orbital exenteration cavity using scapular tip flaps has been reported.56 Careful preoperative planning and intraoperative positioning can allow simultaneous tumor resection and flap harvest.

Surgical Technique and Considerations

- Scapular tip osteocutaneous free flap is based on the angular branch of the thoracodorsal artery. After branching from axillary artery, the subscapular artery gives rise to the circumflex scapular and the thoracodorsal arteries (Fig. 21.12 a,b). It should be noted that occasionally the angular branch does not arise from the thoracodorsal artery, but from another artery in the subscapular system (i.e., serratus branch) and careful identification of all vessels prior to ligation is recommended.
- A bone stock of 6 to 14 cm can be safely harvested.58
- The anterior border of the latissimus dorsi muscle is identified. The thoracodorsal artery can be identified on the anterior edge and under the surface of the muscle. The serratus branch can also be visualized on the surface of the serratus muscle. The angular branch will generally originate from the thoracodorsal or serratus branch and can be seen passing along the lateral border of the scapula.
- The scapular tip of osteocutaneous flap has a long pedicle length decreasing the need for vein grafts and associated added morbidities.57 It can be modified to include the serratus anterior or the latissimus dorsi muscles and skin paddles for complex composite orbital or midface reconstruction.
- The scapular tip also has excellent contour for orbital floor or malar eminence reconstruction.56
- The harvest of the flap requires the patient to be in a semidecubitus position and may preclude simultaneous extirpation and flap elevation; however, a two-team approach has been described with the patient in a pelvic rotation.58

Perioperative Management

Postoperative donor-site morbidities are reasonable, and early physiotherapy and mobilization can help to prevent shoulder disabilities.56,57 Most patients maintain excellent function; however, in cases where large quantities of bone and latissimus muscle are harvested, donor site morbidity may include dysfunction of the shoulder in terms of strength and mobility, especially when reaching above the head.

Orbital Prosthesis

After orbital exenteration, an open cavity can be created and fitted with an orbital or ocular prosthesis at a later date. Open
cavity reconstruction allows for the added benefit of tumor surveillance; however, hollowed appearance of the orbital exenteration cavity can be aesthetically unpleasing.\(^5\)

If an open exenteration cavity is elected, the eyelid and conjunctiva structures should be preserved when oncologically possible to maximize aesthetic outcome. Reconstructive options include skin graft, locoregional pedicled flaps such as temporalis muscle or temporoparietal fascia flaps, or a thin and pliable radial forearm fasciocutaneous flap.

**Note**

If an open exenteration cavity is elected, the eyelid and conjunctiva structures should be preserved when oncologically possible to maximize aesthetic outcome.

If an orbital prosthesis is elected, patient should understand the osseointegrated implants required for prosthesis retention that require routine care and occasional replacement, which can be prohibitively expensive, leading to patients abandoning its use.\(^6\)\(^,\)\(^6\)\(^1\) Wearing glasses can improve the appearance of orbital prosthesis by creating a “frame” around the prosthesis to distract the asymmetry.

It is essential to have a frank discussion of an open versus closed exenteration cavity preoperatively, in order to determine a patient’s wishes and expectations.

### 21.7 Conclusion

As experience continues to grow with the use of transnasal endoscopic approaches, novel reconstructive techniques continue to evolve. Many lesions that were once relegated to open craniofacial resections can now be safely and expeditiously reconstructed with endonasal techniques. The same principles that are used for open techniques have been maintained in endoscopic approaches allowing for similar complication and success rates. With continued experience and improvement in technology, patient outcomes can continue to improve.

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22.1 Anatomy of the Nasopharynx

The nasopharynx is the region located behind the nasal cavities and above the soft palate. The undersurface of the body of the sphenoid bone forms the slanting roof that merges inferiorly with the posterior wall, which is formed by the arch of the atlas and the upper part of the body of the axis vertebra. The floor of the nasopharynx opens downward into the oropharynx at the level of the soft palate. The lateral wall is formed by the superior constrictor muscle with the opening of the eustachian tube situated in the upper part. The cartilage that surrounds the orifice of this auditory tube is an incomplete ring, deficient in the inferolateral portion. The medial portion of the cartilage elevates the mucosa to form the medial crura. The slit-like space situated medial to this crura is the fossa of Rosenmüller; its size and depth varies between individuals, and nasopharyngeal carcinoma (NPC) is commonly found in this recess.

The posterior wall of the nasopharynx is lined with stratified squamous cell, and pseudostratified ciliated epithelium is found in the region of the nasopharynx near the choana. The epithelium lies on a well-defined basement membrane and then the lamina propria, which contains abundant lymphoid tissue. The superior constrictor forms the muscular layer of the nasopharynx, investing this muscle on the outside is the pharyngobasilar fascia. This fascia joins its counterpart from the opposite side to form the median raphe, which extends from the skull base to the posterior pharyngeal wall. The superior constrictor is absent in the superior part of the nasopharynx, from the superior clivus to the roof of the nasopharynx, where the pharyngobasilar fascia directly wrapped around the mucosa. The pharyngobasilar fascia together with the prevertebral fascia encloses the retropharyngeal space, which harbors the node of Rouviere. This retropharyngeal space is part of the retrostyloid space of the para-nasopharyngeal space (Fig. 22.1). The last four cranial nerves, the carotid sheath, and the sympathetic trunk are located in this retrostyloid space, and they can be affected by direct tumor extension or lymphatic permeation. Important structures located in the prestyloid space are the maxillary artery and nerves.

The lymphatic supply of the nasopharynx is found mainly in the submucosal region, which drains into the retropharyngeal lymph nodes. Efferent from these nodes together with some lymphatics that come directly from the nasopharynx drain to the deep cervical lymph nodes. The lymphatic drainage then goes in an orderly fashion, from the high neck nodes to the lower ones, and this is also the pattern of metastasis of NPC in the cervical lymph nodes.1

Note

Cranial nerves IX, X, XI, and XII and the sympathetic trunk are located in this retrostyloid space. Tumor extension can present as a deficit in one or more of these cranial nerves.

Note

The retropharyngeal lymph nodes are the first echelon nodal group in NPC; however, level II adenopathy is a more common clinical manifestation of neck disease.

22.2 Histopathology

Most of the malignancy of the nasopharynx originated from the mucosa, though other types of malignancy including lymphomas and sarcomas can occur in the nasopharynx. NPC is a squamous cell carcinoma (SCC) with a varying degree of differentiation, arising from any part of the epithelial lining of the nasopharynx, most frequently from the fossa of Rosenmüller, the recess located medial to the medial crura of the eustachian tube. The World Health Organization (WHO) classified NPC into three subtypes: well-differentiated keratinizing SCC (WHO type I), nonkeratinizing carcinoma (WHO type II), and undifferentiated carcinoma (WHO type III).2Histologically, the well-differentiated subtype is similar to other well-differentiated SCCs in the upper aerodigestive tract, with malignant cells showing squamous differentiated and keratinization. In contrast, the malignant cells of the nonkeratinizing and undifferentiated subtype of NPC are large polygonal cells with a syncytial character. These cells are frequently intermingled with lymphoid cells in the nasopharynx, giving rise to the term lymphoepithelioma.3 Electron microscopy studies have, however, confirmed the squamous origin of these malignant cells. These tumor-infiltrating lymphocytes are predominately T cells and CD8+.4

In North America, around 25% of NPC patients have type I histology, 12% type II, and 63% type III. The respective histological distribution in Chinese patients is 3, 2, and 95%, respectively.5

Note

Type III undifferentiated nasopharyngeal carcinoma is the most common of NPC in North America.

22.3 Epidemiology and Etiology

The incidence of NPC in general is three times more in men than in women and this ratio is the same in high-incidence area and lower-incidence area. The median age is 50 years—10 to 15 years younger than most smoking-related head and neck cancers. There exists a wide variation of incidence of NPC among different ethnicity and locality. NPC is frequently seen in the inhabitants of southern China, northern Africa, and Alaska. In 1980s, the reported incidence of NPC among men and women in Hong Kong, which is geographically adjacent to Guangdong Province in southern China, was 30 per 100,000 and 20 per
100,000, respectively. There is a gradual decline in incidence of NPC in Hong Kong. In 2013, the incidence had dropped to 13.7 per 100,000 in men and 4.8 per 100,000 in female. This malignancy is, however, uncommon in other countries; the age-adjusted incidence for both sexes is fewer than 1 per 100,000.

Apart from Southern China, Malaysia and Indonesia have high incidence of NPC. North Africa, especially people from Tunisia and Algeria, also has high incidence of NPC. Native peoples in North Canada and Greenland, the Intuits, are another ethnic group with high incidence of NPC.

The incidence of NPC still remains high among Chinese who have immigrated to Southeast Asia or North America but is lower among second- and third-generation Chinese born in North America when compared with those born in southern China. Migrants from low-incidence areas to high-incidence areas do have increased risk of NPC. Approximately 10% of the NPC patients have familial clustering of cases. The first-degree relatives of NPC patients have a six times greater chance of developing NPC than controls. Thus genetic, ethnic, and environmental factors may all play a role in the etiology of the disease.

Apart from genetic susceptibility, one commonly suggested etiologic factor is the consumption of salted fish. Dimethylnitrosamine, a carcinogenic compound, has been detected in the salted fish, and had been suggested as a cause of NPC. Subsequent case-control study, however, showed that frequent consumption of salted fish before 10 years of age was associated with increased risk of developing NPC.

One special feature of the endemic type (poorly differentiated type) of NPC is the near universal presence of Epstein-Barr virus (EBV) genome in the cancer cells. As EBV is present in many races of the human population, it is unlikely that EBV is the only causative agent of NPC. Genetic studies like comparative genomic hybridization studies have demonstrated alterations in multiple chromosomes such as the deletion of regions at 14q, 16p, 1p, and amplification of 12q and 4q. Tumor suppressor genes have also been recently located in chromosome 14q. This suggests that genetic factors have an important etiologic role in NPC.

Note

The incidence of NPC still remains high among Chinese who have immigrated to Southeast Asia or North America but is lower among second- and third-generation Chinese born in North America when compared with those born in southern China.

Note

NPC carcinogenesis is a series of complex events starting with genetic susceptibility, followed by EBV infection and environmental carcinogens leading to development of the cancer.

The exact sequence of events in the carcinogenesis of NPC has not been thoroughly understood. NPC carcinogenesis is a series of existing complex events starting with genetic susceptibility,
followed by EBV infection and environmental carcinogens leading to development of the cancer.21

### 22.4 Presentation

Symptoms are related to the location of the primary tumor, their infiltration of structures in the vicinity of the nasopharynx, or metastasis to the cervical lymph nodes. They can be classified into nasal symptoms, ontological symptoms, neck symptoms, and neurologic symptoms. Nasal symptoms included epistaxis, nasal obstruction, and blood-stained nasal discharge and are related to the presence of tumor mass in the nasopharynx. Otologic symptoms included unilateral hearing loss, tinnitus, and blockage sensation of the affected ear. These neurologic symptoms are likely the result of dysfunction of the eustachian tube, caused by posterolateral extension of the tumor to the para-nasopharyngeal space. Serous otitis media was noted in 41% of 237 newly diagnosed NPC patients. Thus, when a Chinese adult patient or any patient from a high-incidence area presents with serous otitis media, the possibility of NPC should be considered.22

A headache or multiple cranial nerve neuropathies including cranial nerves III, IV, V, and/or VI may be a result of superior extension of the tumor into the skull base, causing these neurologic symptoms. Many patients presented with nodal metastasis as the symptom of presentation. Neck masses usually appear first in the upper neck due to metastasis to the cervical lymph nodes (Fig. 22.2). As the nasopharynx is located in the midline, it is not uncommon to see patients presenting with bilateral cervical lymph nodes.

**Note**

An adult Chinese patient who presents with serous otitis media should always be carefully evaluated for the possibility of NPC.

Many of these symptoms are inconspicuous and nonspecific; the painless, enlarged lymph nodes are frequently under the cover of the sternocleidomastoid muscle and remained unnoticed until they reach a significant size. Thus, many patients suffering from NPC only seek medical advice when the...
disease is in the advanced stage. A retrospective study of 4,768 patients reported that the symptoms at presentation were neck mass in 76%, nasal symptoms in 73%, aural symptoms in 62%, and cranial nerve palsy in 20% of patients.

NPC presenting with distant metastasis is uncommon and is usually associated with advanced local disease or multiple nodal metastasis. Common sites of metastasis included the bone, liver, and lung.

A rare form of presentation of NPC is the paraneoplastic syndrome of dermatomyositis. Up to 12% of patients suffering from dermatomyositis may have NPC or develop NPC in the future.

22.5 Diagnosis and Workup

Patients, especially from high-incidence area presented with above symptoms suggestive of NPC should be thoroughly evaluated for NPC. Unfortunately, the nasopharynx is situated deep inside the skull and is difficult to examine without specialized equipment. A good history, together with a thorough clinical examination including endoscopy of the nasopharynx, is the basis for making the diagnosis. In a majority of the patients, endoscopy would reveal the presence of a tumor mass in the nasopharynx and the mass should be biopsied for histological diagnosis. Rarely, patients with NPC may have a relatively normal nasopharynx on endoscopy and the diagnosis will require additional investigations.

A good history, together with a thorough clinical examination including endoscopy of the nasopharynx, is the basis for making the diagnosis of NPC.

Cross-sectional imaging by computed tomography (CT; Fig. 22.3) or magnetic resonance imaging (MRI; Fig. 22.4) may show abnormal structural alterations in the nasopharynx and its vicinity. The neck should also be included in the imaging studies for the detection of occult metastasis to the neck. Serology test showing elevated EBV immunoglobulin A (IgA) antibodies will give further grounds for suspicion and would justify an endoscopic examination and a biopsy of the nasopharynx.
definitive diagnosis of NPC requires a positive biopsy taken from the tumor in the nasopharynx. When there are palpable cervical lymph nodes, fine-needle aspiration (FNA) cytology should be performed. Even when there are no clinically enlarged neck lymph nodes, the neck lymph nodes should be investigated for any occult metastasis. An ultrasound examination of the neck is an inexpensive modality that can detect occult nodal metastasis and any suspicious nodes should have FNA cytology examination under ultrasound guidance.25 Alternatively, a positron emission tomography (PET) scan can also detect occult nodal metastasis, especially in retropharyngeal region, which is not accessible to the ultrasound scan.26 This will give additional information as to the extent of disease at the time of presentation.

**Note**

Serology testing demonstrating elevated EBV IgA antibodies is the ground for suspicion of NPC and should prompt an endoscopic examination and a biopsy of the nasopharynx.

### 22.5.1 Endoscopic Examination

The nasopharynx can be adequately examined under topical anesthesia with either the rigid or flexible endoscope (Fig. 22.5). A 5% cocaine is a good choice for topical anesthesia as the cocaine has both local anesthetic and vasoconstriction properties. However, cocaine has cardiovascular toxicities and also a controlled substance. If cocaine is not available, a mixture of topical anesthetic like 2 to 5% lidocaine with a nasal decongestant like 1:10,000 adrenaline, 0.5% phenylephrine or 0.1% oxymetazoline with also offer excellent local anesthesia and decongestion of the nasal cavity mucosa. The rigid Hopkin endoscope is 4 mm or smaller in diameter, and both the 0- and 30-degree scopes give an excellent view of the nasopharynx and tumor on the side of insertion (Fig. 22.6). A 70-degree endoscope inserted behind the soft palate allows visualization of the roof of the nasopharynx and both eustachian tube openings and provides a good view of extension of the tumor across the midline (Fig. 22.7). These telescopes, however, do not have a suction channel, and the biopsy forceps have to be inserted by the side of the endoscope for a biopsy.

The fiberoptic flexible endoscope on the other hand allows thorough examination of the entire nasopharynx even when it is inserted through one nasal cavity. It has a suction channel for the removal of nasal secretions during examination, and biopsy forceps can be inserted through this channel to take a biopsy of the tumor under direct vision. It can also be manipulated upward behind the soft palate to examine the nasopharynx from the inferior aspect. In view of the size of the endoscope and its flexibility, it is well tolerated by most patients. Previous generations of fiberoptic flexible endoscopes had inferior optics compared to that of the rigid endoscope but new flexible video endoscope with high-definition images produces comparable images. The disadvantage of the flexible endoscope biopsy forceps is the small cup size of the biopsy forceps and the small amount of tissue obtained for histological examination may be suboptimal. Thus, multiple biopsies might have to be taken to increase the yield. Occasionally, the NPC may be located in the submucosal region, thus the mucosal surface has to be broken with the forceps to enable deeper tissue to be obtained.27

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Fig. 22.5 Fiberoptic flexible endoscopic views. (a) Normal nasopharynx of right side. Eustachian tube opening (curved arrow) and fossa of Rosenmüller (straight arrows). (b) Tumor arising from the fossa of right side. Eustachian tube opening (curved arrow) and tumor (straight arrow).
Note
When performing a biopsy of the nasopharynx, multiple biopsies are often necessary to achieve an adequate tissue sample to yield a diagnosis.

22.5.2 EBV Serology and Plasma EBV DNA Titer

The special relationship of EBV with NPC also provides a diagnostic tool for NPC diagnosis. In patients suffering from NPC, the antibody IgA responds to the early antigen (EA), and the viral capsid antigen (VCA) of EBV has been shown to be of diagnostic value. The IgA anti-VCA is more sensitive but less specific than the IgA anti-EA. Previous population screening studies of more than thousands of apparently healthy individuals, for those with elevated titers of these antibodies, their incidence of harboring subclinical NPC ranged from 3 to 5%. The value of EBV serology in the diagnosis of NPC was confirmed by population-based retrospective study. In this study, the initial EBV serologies of 9,699 subjects were cross-checked against the cancer registry and death registry in the ensuing 15-year period. It was found that the longer the duration of follow-up, the greater the difference in the cumulative incidence of NPC between seropositive and seronegative subjects. The level of IgA anti-VCA has also been shown to be related to the stage of the disease, and the level may decrease after therapy, but another study has found weak relationship between IgA anti-VCA level and stage of disease. Improvements in molecular biology techniques have allowed quantification of cell-free DNA levels of the EBV genome in the plasma of NPC patients. The plasma EBV DNA titer is more sensitive and specific in diagnosing NPC than EBV IgA serology. Furthermore, the plasma EBV DNA level has prognostication purpose, predicting distant failures. However, it has a moderate sensitivity for the detection of recurrent tumor after radiotherapy, especially when the primary tumor is small.

Note
Plasma EBV DNA titer is sensitive and specific in diagnosing NPC than EBV IgA serology.

22.5.3 Imaging Studies

Cross-sectional imaging is essential to the workup of NPC for treatment. The current staging of NPC heavily depends on the findings in cross-sectional imaging instead of clinical findings alone. Cross-sectional imaging studies provide information on the deep extension of the tumor including skull base erosion and intracranial spread. These investigations are essential nowadays to document the extent of the disease in the nasopharynx and in the planning of delivery of radiation. This is particularly applicable nowadays as intensity-modulated radiation therapy (IMRT) is the standard of care. IMRT delivers targeted radiation more accurately to the tumor while at the same time sparing adjacent normal tissues. MRI is essential in the delineation of the extent of tumor involvement and volume for the planning of IMRT (Fig. 22.8).
CT is able to demonstrate the soft tissue extent of the tumor in the nasopharynx and into the para-nasopharyngeal space. It is sensitive in detecting bone erosion especially that of the skull base. Tumor extension intracranially through the foramen ovale with the perineural spread can also be detected and provides evidence of cavernous sinus involvement without skull base erosion (Fig. 22.9). CT is capable of showing bone regeneration after therapy, and this indicates complete eradication of tumor.

Note
Cross-sectional imaging studies provide information on the deep extension of the tumor including skull base erosion and intracranial spread and should be ordered for newly diagnosed patients.

MRI is now the standard imaging modality for staging of NPC because it can differentiate tumor involvement from inflammation of soft tissues. The advantage of MRI especially with regard to NPC is the better soft tissue differentiation. It can differentiate tumor involvement from inflammation of soft tissues. MRI is also more sensitive at evaluating retropharyngeal and deep cervical nodal metastases (Fig. 22.10). MRI is able to detect bone marrow infiltration by tumors, whereas CT cannot detect this kind of infiltration unless there is associated bony erosion. It is important to detect this marrow infiltration, as it is associated with an increased risk of distant metastases. MRI, however, is unable to evaluate details of bone erosion, and CT should be performed when the status of the base of the skull needs to be evaluated.

Note
MRI is now the standard imaging modality for staging of NPC because it can differentiate tumor involvement from inflammation of soft tissues.
Recurrent NPC after radiotherapy may exhibit a range of signal intensities, and these can be difficult to interpret. Both CT and MRI, however, have relatively low sensitivity in detection of tumor recurrence. PET has been shown to be more sensitive than cross-sectional imaging studies in detecting persistent and recurrent NPC, both at the primary site and in the neck (Fig. 22.11). Unfortunately, osteoradionecrosis in the nasopharynx can cause false-positive results in PET scan.

**Note** PET has been shown to be more sensitive than cross-sectional imaging studies in detecting persistent and recurrent NPC.

### 22.6 Staging

Historically, there were several staging systems that have been used for NPC. The Ho system was often used in Asia, whereas the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) systems are more frequently used in Europe and the United States. The nodal classification in Ho’s staging system has been shown to reflect prognostic evaluation, but its stratification of the T stages into five levels differs from most staging systems for cancer.

Studies in the 1980s and 1990s identified some factors that have prognostic significance such as skull base erosion, involvement of cranial nerves, primary tumor extension to paranasopharyngeal space, and the level and size of the cervical nodes. There was a major revision of the staging system, taking all these factors into consideration. This major revision was reflected in the fifth AJCC/UICC staging system that was published in 1997.

With this new staging system, the T stage has included local tumor extension such as involvement of the nasal fossa, oropharynx, or paranasopharyngeal space. The erosion of skull base, the involvement of infratemporal fossa, orbit, hypopharynx, and cranium or the cranial nerves were all incorporated. The nodal staging has also been revised, and the new staging system has been shown to reflect more precisely patient survival.

With the wide adoption of newer treatment modalities like IMRT, the staging system was revised in 2010 to reflect the improvement in treatment outcome. Prognostic factors like nasal fossa involvement and oropharyngeal extension now can be adequately treated with newer radiation techniques and thus both nasal fossa and oropharyngeal extension were classified as stage 1. With widespread use of MRI, retropharyngeal node involvement can now be easily determined. It has been demonstrated that retropharyngeal node involvement has a prognostic implication and retropharyngeal nodal involvement...
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22.7 Treatment

As NPC is radiosensitive, radiotherapy alone has been employed as the primary treatment modality for decades both for early and advanced stages of the disease. In last 15 years, we see a major advancement in the treatment of NPC with radiotherapy, improving the cure of the disease and reducing the morbidities of treatment. The two major advancements are the use of IMRT and addition of concurrent chemotherapy during radiation therapy.

22.7.1 Radiotherapy

Radiotherapy is the standard treatment for NPC. Radical radiotherapy should be attempted even with the most advanced locoregional disease, as long as there is no evidence of distant metastases; cure is still a realistic goal. The target volume of radiotherapy includes the primary tumor in the nasopharynx and the involved neck nodes. Because of the high incidence of occult metastases to the cervical lymphatics, prophylactic neck irradiation is a standard for the N0 cases.60 Good locoregional control should be the prime objective of treatment, as locoregional relapses represent a significant risk factor for the development of distant metastases.59

Conventional two-dimensional (2D) radiotherapy employed lateral opposing fields for radiation of the nasopharynx and upper cervical lymphatics. The lower neck lymphatics are treated with anterior cervical field.60 The major limitation to delivering higher dose radiation is the tolerance of the spinal cord, which should be limited to 40 to 45 Gy. The disadvantage of 2D radiation is the potential for underdose in the parapharyngeal space and the junction between the nasopharynx field and upper cervical lymphatics.

IMRT is now the standard of care for NPC in many centers. IMRT employs multiple beams (seven to nine) of radiation with alternating intensity to deliver the prescribed radiation dose to the target area while keeping the designated vital structures below the toxic dose. The radiation oncologist first designates the gross tumor volume (GTV) as seen on cross-sectional imaging in the planning computer. MRI is the primary imaging
modality for planning but can be fused with CT and/or PET/CT for planning purpose. Then the clinical target volume (CTV) is planned, which included the GTV plus areas of subclinical disease spread around the nasopharynx and the neck lymphatics. Finally, a planning target volume (PTV) is defined, which is the CTV plus a margin to allow for errors in patient positioning movements of anatomical structures. Finally, the areas and dose limits of vital structures like the brainstem, spinal cord, optic nerves, pituitary gland, and cochlear and parotid glands will be marked on the scans. The planning computer will generate a radiation plan and the radiation oncologist will decide if the radiation plan is acceptable (Fig. 22.12). The GTV would usually receive up to 70 Gy in 2 Gy per fraction while the CTV will receive up to 60 to 66 Gy. With IMRT, the local control rate for T1–T2 tumors is reported to be over 90%, while toxicities commonly seen in 2D radiotherapy like temporal lobe necrosis, trismus, xerostomia, and hearing loss were reduced.

### Note
With IMRT, the local control rate for T1–T2 tumors is reported to be over 90%.

### Acute Side Effects
During radiotherapy, patients often experience the sensation of dry mouth starting at the end of the first week, and the degree
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of dryness will progress toward the end of radiotherapy. For most patients, the dryness of mouth becomes permanent if the conventional 2D planning of radiotherapy treatment was used. With the use of IMRT and sparing the contralateral parotid gland, some return of salivary function can be expected 2 years after radiotherapy.65 Mucositis involving the posterior part of the oral cavity and the upper part of the oropharynx usually appears toward the end of the fourth week of radiotherapy, and this will progress toward the end of radiotherapy. The use of concurrent chemotherapy greatly aggravates the mucositis. The mucositis, however, will improve within a few weeks after completion of radiotherapy. Treatment of mucositis is mainly supportive such as the use of gargle and analgesic. Gabapentin is reported to be especially effective in relieving the pain from mucositis, especially in patients undergoing concurrent chemoradiation.66 For a small percentage of patients, when the mucositis affects adequate oral feeding, nasogastric tube feeding may be required.

Note

Gabapentin is reported to be especially effective in relieving the pain from mucositis, especially in patients undergoing concurrent chemoradiation.

Late Sequelae of Therapy

Unfortunately, because of the location of the nasopharynx, it is in close proximity to several radiosensitive, dose-limiting organs. These are the brainstem, temporal lobes, pituitary–hypothalamic axis, middle and inner ears, spinal cord, eyes, and parotid glands. Radical radiotherapy when including these organs may produce undesirable complications. The radiation field sometimes has to include these organs in view of the infiltrative behavior of NPC and the proximity of tumor extension to these organs especially when disease is advanced. The use of IMRT has reduced the radiation dose to these vital structures but in advanced tumors it is difficult to protect these structures without reducing the radiation delivered to treat the primary tumor. These sequelae of radiotherapy for NPC include hearing loss,67 osteoradionecrosis of the temporal bone,68 neuroendocrine complications,69 dry mouth, poor oral and dental hygiene,70 radiation-induced soft tissue fibrosis,71 and carotid artery stenosis.72 Dysphagia is a common complication after treatment of NPC and some patients may need long-term nonoral feeding.73,74 The most debilitating sequelae are the neurologic complications. These may include serious disorders such as temporal lobe necrosis,75 and cranial nerve palsies,76 and less obvious effects such as memory,77 cognitive,78 and neuropsychological dysfunctions.79 The use of chemotherapy in more advanced cases further augments the side effects, which include ototoxicity and peripheral neuropathy associated with cisplatin.80

22.7.2 Adjuvant Chemotherapy to Radical Radiotherapy

Chemotherapy has been used as neoadjuvant or adjuvant treatment in advanced stage NPC. The Intergroup 1997 study was the first study to demonstrate that the use of concurrent chemoradiotherapy (i.e., three courses of adjuvant chemotherapy in addition to initial chemoradiotherapy) improved overall survival when compared with radiotherapy alone.81 The meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC) showed survival benefit with the use of chemotherapy in addition to radiotherapy in treatment of NPC. The effect of additional chemotherapy is most pronounced when used in a concurrent setting, with a hazard ratio of 0.6.82 In 2014, the meta-analysis was updated with a total of 19 trials and 4,798 patients. Addition of chemotherapy showed a significant improvement in overall survival, with a hazard ratio of 0.79.83

Cisplatin is the standard chemotherapeutic agent used for concurrent chemoradiation. It can either be given as a weekly 40 mg/m² regime or as a three weekly 100 mg/m² regime. A total dose of 200 mg/m² administered during radiotherapy was required to benefit survival.

Despite the use of concomitant chemoradiotherapy, distant metastases remain the major cause of failure,45,84 and the prognosis for stage IV patients remains grim.85 Trials have shown a survival benefit with concurrent chemoradiation followed by adjuvant chemotherapy in overall survival,86,87 but the exact benefit of adjuvant chemotherapy is not known. One phase III study failed to show any benefit of adjuvant chemotherapy after concurrent chemoradiation.88 Because of the poor tolerance of patients to further adjuvant chemotherapy after concomitant chemoradiotherapy, the use of induction chemotherapy to be followed by concurrent chemoradiotherapy has also been studied. The preliminary results of a recent trial showed no definite gain in switching from a concurrent–adjuvant chemotherapy regimen to an induction-concurrent regime.89 However, this does not mean induction chemotherapy does not have any role in managing advanced stage NPC. In high T-stage NPC, induction chemotherapy can shrink the tumor, improving the radiation coverage of the tumor and reducing the dose of radiotherapy to adjacent vital structures.90

Note

Despite the use of concomitant chemoradiotherapy, distant metastases remain the major cause of failure.

22.7.3 Chemotherapy for Metastatic and Advanced Recurrent Nasopharyngeal Carcinoma

Cisplatin-based combination chemotherapy is the most effective treatment for metastatic NPC. Cisplatin and incisional 5-fluorouracil (5-FU) has become the standard treatment, achieving a 66 to 76% response rate.91 Phase II studies on the newer agents including capecitabine, gemcitabine, ifosfamide, paclitaxel, and irinotecan have shown benefit of these agents when platin-based chemotherapy had failed.92,93 Combinations of two or three of these newer agents have the potential of improving the response rate but at the expense of increased toxicities.

It is generally agreed that treatment of metastatic NPC using chemotherapy is essentially palliative, though long-term disease-free survivors have been reported.94 For selected
patients with limited metastases (oligometastases), more aggressive additional local treatment can be considered. Resection of lung metastases may result in prolonged control for patients where the spread of the carcinoma to the lung has been limited.95,96 When there is limited spread to the mediastinal nodes, the addition of radiotherapy to chemotherapy may also result in more prolonged tumor control.97 Solitary liver metastasis can be treated with liver resection or radiofrequency ablation if the location of the metastasis is favorable.98

### 22.7.4 Treatment of Recurrence

Despite the fact that concomitant chemoradiation has improved the outcome of patients suffering from NPC, there are some patients who still develop local or regional recurrence after the initial radical chemoradiation management. These failures could present either as persistent or recurrent tumor. When the tumor did not regress completely after therapy or reappeared within 6 months after treatment, it was recognized as persistent tumor. For recurrent disease, the tumor showed complete regression after treatment and reappeared only 6 months after completion of treatment.

To successfully manage these persistent or recurrent diseases in the nasopharynx, early detection is essential. The PET is superior both to CT99 and MRI100 though false-positive results can occur in patient suffering from osteoradionecrosis instead of recurrent tumor.99 Therefore, an endoscopic examination with biopsy should be performed to confirm the presence of malignancy in the nasopharynx. Persistent or recurrent tumor in the neck node after chemoradiotherapy, however, is notoriously difficult to confirm, as in some lymph nodes only clusters of tumor cells are present.101 Thus, FNA cytology aiming to confirm the presence of malignant cells in the nodes is frequently not helpful. The clinical course of the neck node and the findings of PET scan guide the clinician toward further management of these patients. Plasma EBV DNA titer offers another tool for monitoring treatment response and detecting recurrence. If the disease has completely resolved after primary chemoradiation, plasma EBV DNA titer should not be detectable after treatment. Any persistently elevated plasma EBV DNA titer should lead to the suspicion of incomplete response or development of distant failure.102,103

### Note

Resection of lung metastases may result in prolonged control for patients where the spread of the carcinoma to the lung has been limited.

Locally or regionally persistent or recurrent NPC should be treated whenever possible, because although survival after salvage treatment for extensive disease remains poor, the outcomes of these patients were still superior to those of patients who were given supportive treatment only. Even for those NPC patients with synchronous locoregional failures, aggressive treatment should also be considered for selected patients.104

#### Persistent or Recurrent Tumor in Neck Lymph Nodes

Since the introduction of concurrent chemoradiation for NPC, the incidence of isolated failure in the neck node had dropped to less than 5%.105 For patients with neck nodes harboring the malignant cells when managed with a second course of external radiotherapy, the reported overall 5-year survival rate was only 19.7%.106 Radical neck dissection is still the recommended form of surgical salvage even though the persistent or recurrent disease in the neck after radiotherapy presents with only one clinically palpable lymph node, and simple excision of the lymph node might be considered sufficient for tumor eradication. Pathology studies of the serial sectioning of the neck dissection specimens obtained from these patients, however, have shown that for those with persistent or recurrent cervical lymph nodes in the neck, the extent of tumor involving local tissue was extensive. There were three times more pathologic lymph nodes in the neck than what could be detected at clinical examination. There was a 70% incidence of extracapsular spread among the malignant nodes. The affected nodes were closely associated with the sternocleidomastoid muscle, spinal accessory nerve, and the internal jugular vein. Thus, in ensuring the removal of all the tumor-bearing nodes in the neck, a radical neck dissection was considered essential for salvage. Under this clinical situation, the radical neck dissection should be performed to achieve the best outcome.107 Radical neck dissection as a salvage for isolated nodal recurrence in NPC has been reported to achieve a 5-year local tumor control rate of 66% in the neck and a 5-year actuarial survival of 38%.107 Recent publications have challenged this philosophy, which was based on histological studies done before the introduction of concurrent chemoradiation.108 One study showed that level I can be spared for salvage neck dissection in isolated nodal recurrence of NPC.108

When tumor in the neck node extends beyond the confines of the lymph node, then radical neck dissection may still fail to remove all malignant tissue. To achieve a similar tumor control rate as when radical neck dissection was performed for less extensive neck disease, further therapy to the tumor bed is essential. This includes further external radiotherapy or brachytherapy. Afterloading brachytherapy has been used and has achieved acceptable results.109 Hollow nylon tubes were placed accurately on the surgical bed at the completion of the radical neck resection, and single-source, high-dose-rate iridium wires were inserted after the neck wound had healed as the afterloading brachytherapy radiation source. As the neck skin was included in the initial radiation field and could not stand further radiation, the skin overlying the planned brachytherapy area should be removed and replaced. The reconstruction of the neck skin is achieved with either a deltopectoral flap or a pectoralis major myocutaneous flap. The former provides full-thickness skin coverage and requires a second-stage operation 3 weeks later to return the deltopectoral flap to the anterior
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Carcinoma of the nasopharynx is a tumor of the nasopharynx. The nasopharynx is situated in the central part of the head. Tumor located in the region and its vicinity is difficult to be amenable for retreatment.111 Salvage treatment for local failures can be in the form of external radiotherapy, brachytherapy, or surgical resection. Retreatment for local failures is moderately successful, a large survey of 200 local failures treated with different modalities showed an overall 3-year survival of 74%.111 Retreatment poses a challenge for clinicians as the patients had already exposed to the toxicities of previous treatment.

22.7.5 External Beam Radiotherapy

Traditional 2D external beam radiotherapy has poor success rate for salvaging local failures. One study showed that the 5-year survival of reirradiation for local failures was only 14 and 26% of patients suffered from late sequelae of radiation.112 The main limitation in applying external beam reirradiation is the limited tolerance of vital organs like brainstem, optic chiasma, and temporal lobe to second radiation.

Newer radiation techniques like 3D stereotactic radiation and IMRT can deliver high dose to the local tumor but protect the vital organs from radiation overdose.113,114,115 The reported 5-year overall survival for a series of 30 patients treated with stereotactic radiotherapy was 40% and the local control was 56.8%. About 22.5% of the rT1 and rT2 patients treated with this technique had central nervous system (CNS) complications, but 72.2% of rT3 and rT4 patients treated had CNS complications.114

22.7.6 Brachytherapy

To avoid the radiation complications from second radiation, brachytherapy was employed for reirradiation. When brachytherapy is employed for the management of persistent or recurrent NPC in the nasopharynx, the radiation dose is placed close to or inserted directly into the tumor, delivering high-radiation dose at the brachytherapy source, and the radiation dose then declines with increasing distance from the tumor. Thus, the persistent or recurrent tumor in the nasopharynx receives the highest therapeutic radiation, while the surrounding tissue was irradiated with a much smaller dose. Intracavity brachytherapy has been used traditionally for NPCs both as a boost of the primary treatment and as salvage treatment for persistent or recurrent disease.116 The radiation source such as iridium-192 (192Ir) can be placed in a mold, and this is then inserted into the nasopharynx, delivering 40 Gy for persistent disease and 50 to 60 Gy for recurrent disease. Good local tumor control rates and survival rates have been reported, with a 5-year local control of 68.3% and 5-year overall survival of 46.9%.117 To circumvent the problem of irregular contour of the primary tumor within the nasopharynx, radioactive interstitial implants were used as a brachytherapy source, and these radiation sources were inserted directly into the tumor. Thus, high-dose radiation is delivered to each region of the localized persistent or recurrent tumor in the nasopharynx.118

Radioactive gold grains (198Au) were frequently employed as interstitial implants for brachytherapy. The split-palate approach under general anesthesia has been described for insertion of the radioactive gold grains.119 The soft palate was incised in the midline and lifted with the mucoperiosteum of the hard palate. After the retraction of the palatal flaps, the tumor in the nasopharynx was exposed, and accurate implantation of the desired number of gold grains could be performed under direct vision. Thus, an ideal dosimetry for the radiation of the persistent or recurrent tumor could be achieved. The surgical procedure is simple, and the morbidity related to surgery is low.120 With interstitial gold grain implants in the treatment of persistent and recurrent NPC after radiotherapy, the morbidity related to the second course of radiation is minimal. The 5-year local tumor control rates were 87 and 63%, respectively, and the corresponding 5-year disease-free survival rates were 68 and 60%, respectively. About 16% of patients had persistent palatal fistula.121

The disadvantage of reirradiation with either brachytherapy techniques is the radiation necrosis of the nasopharynx and clivus.

22.7.7 Surgical Treatment

Nasopharyngectomy

Although brachytherapy is less invasive local treatment for salvaging local disease, it can only be applied to salvage small local recurrences, as the penetration of the brachytherapy radiation is limited to 1 to 2 cm. Brachytherapy is also not applicable when the tumor extends either directly to the para-nasopharyngeal space or affects the lymph nodes in this space. Salvage surgery in the form of nasopharyngectomy with resection of lymph nodes in the para-nasopharyngeal space has been shown to be effective to eradicate localized tumor in selected patients. Also, salvage surgery can avoid the complications of excessive radiation to the nasopharynx that brachytherapy is associated with.

Salvage surgery can be employed for recurrent disease that is not amenable to reirradiation.

The nasopharynx is situated in the central part of the head. Tumor located in the region and its vicinity is difficult to be

Note

Good local tumor control rates and survival rates have been reported when brachytherapy is employed for recurrent disease.
exposed adequately to allow an oncologic resection. Few approaches have been reported to be useful in the exposure of the nasopharynx to allow salvage nasopharyngectomy. Superior and posterior approaches are not practical, as the brain and the vertebral column limit the movement of tissue to get good exposure. A lateral approach, the infratemporal fossa approach to the nasopharynx, is the first reported approach for resecting malignant lesions in the nasopharynx.\textsuperscript{122} With this route, a radical mastoidectomy has to be performed and some important structures have to be mobilized; these include the internal carotid artery, the fifth cranial nerve, and the floor of the middle cranial fossa. The resultant morbidities after this approach are not negligible, and considerable surgical expertise is required to carry out this procedure. This approach exposes directly the lateral wall of the nasopharynx including the internal carotid artery on the side of the surgery, thus it is useful for laterally located disease. It, however, does not provide access to the lateral wall of the nasopharynx on the opposite side and access to the nasal cavity.

The transantral and midfacial degloving procedures allow the approach of the nasopharynx from the front but do not provide adequate exposure of the whole nasopharynx, including the superior and lateral walls. These anterior approaches, even with controlled fracture of the hard palate followed by its downward displacement, only expose the posterior wall of the nasopharynx and not its lateral walls and its vicinity where most tumors are located. Instrumentation in the limited space is also difficult. It has been shown that the midfacial degloving approach is less effective than the maxillary swing for oncologic control.\textsuperscript{123}

The nasopharynx can also be approached from the anterolateral route following the lateral swinging hard palate and the maxillary antrum (\textsuperscript{Fig. 22.13}). This maxillary swing approach exposes the nasopharynx and its vicinity adequately to allow salvage nasopharyngectomy. The facial incision employed is similar to that of maxillectomy except that there is no incision along the upper alveolar ridge as the anterior cheek flap is not to be separated from the anterior wall of the maxilla. A total of three osteotomies are required to detach the maxilla. The first horizontal osteotomy on the anterior wall of the maxilla is placed below the inferior rim of the orbit, thus the orbital floor is not disturbed. The oscillating saw then goes through the maxillary antrum to separate the posterior wall of the maxilla from its superior attachments. The second osteotomy divides the hard palate in the midline, and the third osteotomy is to separate the maxillary tuberosity from the pterygoid plates with a curved osteotome. After the osteotomies, the maxilla with half of the hard palate attached to the anterior cheek flap can be swung laterally as one osteocutaneous flap.

\textsuperscript{Fig. 22.13} Schematic CT image. (a) Planned osteotomies of the maxilla and the posterior part of the nasal septum. (b) The maxilla is swung laterally while still attached to the cheek flap.
The operative procedure involved is similar to that of a maxillectomy, only that here the maxilla is left attached to the anterior cheek flap and is returned to its original position after the nasopharyngectomy. A dental plate is usually made before the operation as this ensures the correct repositioning of the maxilla after removal of tumor. For similar reasons, the holes for the titanium plates that would be used to fix the maxilla to the rest of the facial skeleton were drilled before the osteotomies. After the maxilla is swung laterally, pterygoid plates are removed and the attached pterygoid muscles are retracted, then the entire nasopharynx and the para-nasopharyngeal space are exposed to allow an oncologic surgical procedure to be performed. The posterior part of the nasal septum is removed to improve exposure of the opposite nasopharynx. The cartilaginous portion of the eustachian tube together with the lateral wall of the nasopharynx including the fossa of Rosenmüller on the side of the swing is removed with the tumor en bloc. The prevertebral muscle could be removed together with the tumor to improve the resection margin, and for similar reason, the anterior wall of the sphenoid sinus is removed. The sphenoid sinus is opened and its mucosa is not disturbed.

The wide exposure achieved after the maxilla is swung laterally allows the dissection of the para-nasopharyngeal space under direct vision. Thus, lymph nodes or the tumor that has extended to the para-nasopharyngeal space can be removed. The internal carotid artery lying outside the pharyngobasilar fascia can be identified by palpation during the dissection of the para-nasopharyngeal space and thus safeguarded.

The morbidity associated with this salvage surgical procedure is low and acceptable. Many patients developed some degree of trismus after operation. This is related to the previous radical radiotherapy and the development of additional fibrosis after the dissection around the pterygoid muscle region. The trismus frequently improves with passive stretching.

A variation of the maxillary swing approach is facial translocation approach in which the whole maxilla removed as a free bone graft and put back together after completion of the resection in the nasopharynx. The risk of this procedure is variable viability of the translocated facial skeleton, especially after radiotherapy.

When the persistent or recurrent tumor can be resected with a clear margin, the long-term results have been satisfactory. Results from a large series of over 246 patients showed that the 5-year actuarial local control of tumors in the nasopharynx after salvage nasopharyngectomy was 74%, while the 5-year overall survival was 56%.

With advancement of technology in endoscopy, minimally invasive nasopharyngectomy in the form of endoscopic nasopharyngectomy has been developed. The advantages of endoscopic nasopharyngectomy include the absence of a facial scar and minimal disturbance to the muscles of swallowing. Instrumentation and hemostasis would be difficult and frequently alternative energy source devices like laser or plasma knife (Colbator) would need to be employed during dissection.

Endoscopic nasopharyngectomy is usually reserved for resecting small, localized tumors in the nasopharynx (Fig. 22.15), as tissue manipulation with endoscopic instruments is difficult. Most reported case series in the literature had only short follow-up with a 2-year local control rate ranging 70 to 80%. A recently published case–control study with over 100 patients comparing endoscopic nasopharyngectomy with reirradiation with IMRT showed that endoscopic nasopharyngectomy had a superior 5-year overall survival of 77.1 versus 55.5% in reirradiation with...
IMRT. However, no randomized controlled trials has been performed comparing nasopharyngectomy and reirradiation in salvaging recurrent NPC.

A modification of endoscopic nasopharyngectomy is to perform the resection with the aid of the surgical robot. The advantage of employing the robot is the better dexterity of the robotic arms and 3D magnified view offered by the surgical robot, but with the disadvantage of the surgeon losing the tactile sensation. The indication of robotic nasopharyngectomy is similar to endoscopic nasopharyngectomy, currently limiting to small tumors. Early results of robotic nasopharyngectomy are similar to other endoscopic nasopharyngectomy series.

22.8 Clinical Cases

22.8.1 Case 1

T4N0M0 squamous cell carcinoma of the nasopharynx.

Clinical Presentation

A 53-year-old Chinese woman presented with right tinnitus for 3 months, right facial pain and numbness for 2 months. The patient had no other symptoms, and there was no recent change in appetite and body weight. The patient had no prior history of tobacco, and she is a social drinker.

Examination

Clinical examination confirmed palsy of the maxillary division of the right fifth cranial nerve. Otoscopy examination showed right serous otitis media, and tuning fork test confirmed conductive deafness in the right ear. There was no palpable cervical lymph node. Examination of the nasopharynx revealed an exophytic mass in the right fossa of Rosenmüller extending to the right roof. Biopsy of the mass confirmed the presence of undifferentiated carcinoma.

Diagnosis and Workup

Complete blood count and renal and liver function tests were normal, and an antibody against VCA of EBV was elevated at 1:40 dilution, plasma EBV DNA was 1,250 copies/mL. MRI of the nasopharynx confirmed erosion of the clivus and tumor extension through the foramen rotundum and extension to the right middle cranial fossa. There was no evidence of neck node involvement. The patient also had a PET scan performed, which confirmed the extent of tumor in the nasopharynx, and there was no evidence of distant metastases.

The patient had a pure-tone audiogram performed, which showed air–bone gap confirming conductive deafness. Dental examination showed early carious teeth formation in several teeth, and extraction was performed for the two most badly involved teeth, and dental preventive measures were also performed.

Management

As there is significant intracranial extension, in order to minimize the radiation to intracranial structures, neoadjuvant chemotherapy was employed to shrink the tumor and reduce the radiation field. The patient received three cycles of induction chemotherapy consists of cisplatin 100 mg/m² intravenously and 5-F 1,000 mg/m²/d by 120-hour infusion every 3 week. Reassessment MRI scan showed significant shrinkage of the primary tumor.

After induction chemotherapy the patient received concurrent chemoradiation with IMRT. A total tumor dose of 68 Gy in 34 fractions over 7 weeks was given; concomitant intravenous chemotherapy with cisplatin 100 mg/m² was given on days 1, 22, and 43. The radiation dosage to the cervical lymph nodes was 60 Gy.

Assessment of response of tumor at 10 weeks after completion of radiotherapy using endoscope examination showed complete remission of tumor in the nasopharynx, and this was confirmed by biopsy taken from the initial site of tumor. MRI of the nasopharynx performed at 3 months after completion of radiotherapy also confirmed complete remission.

The patient was regularly followed up with clinical examination and endoscope once every 2 months in the first year and every 3 months in the second and third years. MRI of the nasopharynx and neck was repeated every 6 months in the first 3 years, and the patient remained in remission.

22.8.2 Case 2

T1N1M0 squamous cell carcinoma of the nasopharynx.

Clinical Presentation

A 50-year-old Chinese man with history of chronic renal impairment noted a left upper cervical lymph node with no other symptoms.

Examination

Clinical examination demonstrated a 2-cm diameter, firm lymph node in the left upper neck under the cover of the sternocleidomastoid muscle. The node had a smooth surface and
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was mobile. There were no other palpable lymph nodes, and there were no other masses or lesions in the head and neck region.

**Diagnosis and Workup**

FNA cytology showed the presence of metastatic undifferentiated carcinoma and immunohistologic staining for Epstein–Barr virus–encoded small RNAs (EBER) was positive. Endoscopic examination of the upper aerodigestive tract revealed an exophytic growth 0.5 cm in diameter in the nasopharynx obscuring the left fossa of Rosenmüller. Biopsy of the lesion in the nasopharynx showed undifferentiated carcinoma.

**Management**

The patient was managed with radiation with IMRT technique to the nasopharynx and also to both necks. In view of his poor renal function, concurrent chemotherapy with cisplatin was not used but cetuximab was used as concurrent biological therapy instead. About 400 mg/m² cetuximab was given as initial dose on first day of radiation, followed by 250 mg/m² weekly for the duration of the radiotherapy. The total radiation dose to the nasopharynx was 68 Gy and to the neck 64 Gy; these were delivered with daily fractions of 200 cGy over 6 weeks. Complete regression of the tumor in the nasopharynx and the cervical lymph nodes was seen at the fourth week after completion of radiation.

The patient remained asymptomatic for 2 years and then he noticed a progressively enlarging left neck swelling. Clinical examination showed a 2-cm diameter hard mass under the cover of the upper part of the left sternocleidomastoid muscle. The mass was indurated, nontender, and had an ill-defined border. The mass was also attached to underlying structure and thus immobile. The overlying skin, however, was mobile, and there was no other lymph node detected. There was no hoarseness, no swallowing problem, and also no nasal symptom. Endoscopic examination of the nasopharynx revealed normal findings, and both vocal cords were mobile. There was no serous otitis media. PET/CT showed the presence of a 2-cm diameter, enlarged lymph node in the upper neck under the cover of the sternocleidomastoid muscle with increased metabolic activity, while there were no hypermetabolic lesions in the nasopharynx and no evidence of distant metastasis. The CT scan showed no encasement of the carotid arteries by the enlarged neck lymph node but suspicion of invasion of the sternocleidomastoid muscles and levator scapulae muscle by the lymph node (Fig. 22.16). Plasma EBV DNA titer was elevated to 750 copies/mL.

FNA cytology was performed twice and only revealed suspicious cells. In view of the clinical suspicion of recurrent tumor in the neck lymph node on cytology, plasma EBV DNA titer, and PET/CT scan, salvage surgery was planned.

At the time of surgery, incisional biopsy of the neck node was performed first, and frozen section of the specimen confirmed the presence of recurrent tumor in the cervical lymph node. The deep surface of the lymph node was also found to be infiltrating the muscular floor of the upper neck, posterior to the carotid sheath. Radical neck dissection was performed removing the sternocleidomastoid muscle, internal jugular vein, and the accessory nerve. Part of the muscle on the floor of the posterior triangle where the node was attached was also removed together with the skin overlying the area (Fig. 22.17). There was no macroscopic tumor left in the operative field. In view of
the extensive infiltrative nature of the tumor harboring lymph node, parallel hollow nylon tubes separated from each other by 1 cm were placed on the tumor bed (▶ Fig. 22.18). The overlying skin defect was reconstructed with a left pectoralis myocutaneous flap from the left side (▶ Fig. 22.19). The donor site was closed primarily.

Plasma EBV DNA titer was taken on postoperative day 7. The result showed that EBV DNA was undetectable in the plasma. Starting from the eighth postoperative day, iridium wires were inserted into the hollow nylon tubes to deliver a daily dose of 10 Gy to the tumor bed in the neck to a total of 40 Gy. The nylon tubes were removed after completion of brachytherapy. The patient was last seen at 3 years after the radical neck dissection together with the afterloading brachytherapy; there was no evidence of disease. Plasma EBV DNA titer remained undetectable all along after the surgery.

22.8.3 Case 3

T1N0M0 squamous cell carcinoma of the nasopharynx.

Clinical Presentation

A 50-year-old Chinese man presented intermittent blood-stained nasal discharge for 1 month.

Examination

Flexible endoscopic examination demonstrated a mass in the nasopharynx.

Diagnosis and Workup

A biopsy of the mass demonstrated poorly differentiated carcinoma. Clinically, there were no palpable cervical lymph nodes, and subsequent investigation showed no distant metastasis.

Management

The patient was treated with IMRT alone with 66 Gy to the nasopharynx and ipsilateral retropharyngeal lymph node and 60 Gy to bilateral cervical lymphatics.

The patient recovered from the radiotherapy and remained well for 8 months. He then noticed increased postnasal drip associated with altered blood, especially in the morning. Flexible endoscopic examination of the nasopharynx showed a 1-cm diameter mucosal irregularity in the right posterior wall of the nasopharynx; the fossa of Rosenmüller was not involved. MRI showed that the recurrent tumor was superficially localized in the nasopharynx, not infiltrating the prevertebral muscle. Multiple biopsies were performed around the edge of the tumor under direct vision of the flexible endoscope. This was to confirm the extent of the recurrent tumor. In view of the small tumor localized in the nasopharynx, a minimally invasive surgery in the form of robotic-assisted nasopharyngectomy was offered. The nasopharynx was approached by splitting the soft palate in the midline (▶ Fig. 22.20). The soft palate split allowed access of the robotic arms and the tumor was resected with a margin of normal nasopharynx mucosa. The prevertebral muscles were preserved, but the whole periosteum of the upper clivus was removed as deep margin, exposing the bare clivus bone. Frozen-section margins confirmed clear resection margin. A nasoseptal flap was harvested and rotated down to cover the raw bone in the nasopharynx. The palate wound was closed under direct vision in three layers. A nasogastric tube inserted for feeding in the early postoperative period. The
A patient recovered from the operation and did not have any speech or swallowing problem.

**22.8.4 Case 4**
T3N0M0 undifferentiated carcinoma of the nasopharynx.

**Clinical Presentation**
A 40-year-old Chinese man presented with partial right nasal obstruction together and blood-stained postnasal drip for 3 months.

**Examination**
Endoscopic examination demonstrated a tumor originated in the right nasopharynx extending anteriorly to the right nasal cavity causing partial obstruction.

**Diagnosis and Workup**
A biopsy of the mass demonstrated undifferentiated carcinoma. Clinically, there were no palpable cervical lymph nodes. MRI showed tumor in the right nasopharynx with extension to the right nasal cavity. The tumor had infiltrated the right posterior ethmoid sinus. The right pterygopalatine fossa was slightly enlarged, suspicious of tumor infiltration. No enlarged retropharyngeal and cervical lymph nodes were detected on MRI. PET/CT confirmed the extent of disease described by MRI scans. With the presence of paranasal sinus involvement, the disease is staged as T3N0M0.

**Management**
Concurrent chemoradiation with cisplatin and IMRT was employed for curative intent treatment. The local tumor was planned to be treated with 66 Gy, but in order to provide adequate radiation dose to the disease in the posterior ethmoid sinus, the right optic nerve would receive a radiation dose that may cause blindness in the long term. The patient agreed for sacrificing the right vision to improve the local control. Concomitant intravenous chemotherapy with cisplatin 100 mg/m² was given on days 1 and 22 but the patient was unable to receive the 43rd day dose of cisplatin due to neutropenia.

The patient remained well for 36 months and then he noticed repeated episodes of epistaxis, and endoscopic examination revealed an exophytic growth arising from the right fossa of Rosenmüller. Biopsy of the mass confirmed recurrence of the NPC, and subsequent investigations showed no evidence of regional or distant metastasis. MRI showed that the tumor in the nasopharynx and with extension to the para-nasopharyngeal space and suspicion of recurrence in the right pterygopalatine fossa. The recurrent tumor was not close to the internal carotid artery. Although this was quite an extensive rT3 tumor, the recurrent tumor had not involved any vital structures, thus salvage nasopharyngectomy was planned. As the recurrent tumor was close to the eustachian tube, curative resection...
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23 Carcinoma of the Skin of the Head, Face, and Neck

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23.1 Epidemiology

Skin cancer, including both melanoma and nonmelanoma cancer, is the most common cancer in the United States, and the incidence continues to rise. Although the biological behavior of melanoma and nonmelanoma skin cancers (NMSCs) differs, the pathogenesis, anatomical considerations, and fundamental techniques employed in the management of these malignancies are similar. Cutaneous melanoma and aggressive NMSCs of the head and neck require a multidisciplinary approach that involves the judicious application of surgery, radiation, and systemic therapy.

Otolaryngologists and other professionals who care for patients with disorders of the head and neck will increasingly encounter patients with NMSC and cutaneous melanoma. This chapter provides an overview of the optimal management of these lesions. Important differences in the biological behavior of melanoma versus NMSCs, with their resultant treatment implications, are highlighted. By identifying clinical and histopathologic features of aggressive disease, appropriate therapies may be administered, thereby avoiding unnecessary morbidity or toxicity. Surgical techniques that maximize local control with preservation or restoration of function and cosmesis, contemporary strategies for managing the regional lymphatics, and the indications for and options within systemic therapy are described. Because of the increasing frequency of all types of skin cancer of the head and neck, efforts to develop reliable preventive measures and screening programs are also noted, as the keys to halting the growth and impact of this pandemic lie in prevention and early detection.

23.1.1 Nonmelanoma Skin Cancer

NMSC constitutes an epidemic with a potential incidence of 3.5 million cases in the United States, costing $4.8 billion in annual treatment expenditure.\(^1\) This estimate is considered underreported by many as NMSC is not routinely reported to cancer registries. Because of the relationship between ultraviolet light exposure and the development of NMSC, these lesions tend to occur on sun-exposed areas of the body, and 75% arise on the head and neck. The impact of ultraviolet light exposure on the development of NMSC is further accentuated by the increasing incidence of NMSC as degrees of latitude converge toward the equator.\(^4\) Patients, particularly men, over the age of 50 years are generally considered to be at greatest risk of developing NMSC, but recent studies have demonstrated an increase in the incidence of these cancers in women and younger patients.\(^5\) A study originating from the United Kingdom reported a 145% increase in basal cell carcinoma (BCC) among people younger than 30 years between 1981 and 2006.\(^6\) The rising incidence of NMSC in younger patients is accompanied by evidence that aggressive variants of NMSC are becoming more common in younger patients, especially women.\(^7\)

BCC accounts for 80% of NMSCs, and squamous cell carcinoma (SCC) comprises the remaining 20%, while other diagnoses including Merkel cell carcinoma (MCC), sebaceous carcinoma (SC), and others represent approximately 1%.\(^8\) Although more than 95% of NMSCs may be cured by a variety of surgical and nonsurgical therapies, aggressive variants of NMSC exist that are characterized by recurrence, metastases, and increased morbidity.\(^9\) NMSC continues to rise at an estimated 2 to 8% per year with a 100% increase between the periods of 1992 and 2012.\(^10\) These estimates are based on mathematical calculations extrapolating incidence data published between 1971 and 1999. These extrapolations were made because NMSC is not being reported to cancer registries or followed by the Surveillance, Epidemiology, and End Results (SEER) Program. The total number of NMSCs in the U.S. population was estimated to be over 5 million in 2012, while the total number of people being treated for NMSC was at 3.3 million.\(^1\) Mortality estimates for the U.S. NMSC population in 2012, specifically cutaneous SCC, range from 3,932 to 8,791,\(^11\) warranting further evidence that this underrecognized health issue has caused significant morbidity and mortality in this nation. The clinical challenge lies in the early identification of these aggressive lesions to deliver appropriate multidisciplinary care, leading to improved disease control and survival. Clinicians can no longer assume that all NMSCs are created equal.

Note

Nonmelanotic skin cancer continues to rise at an estimated 2 to 8% per year with a 100% increase between the periods of 1992 and 2012.

23.1.2 Cutaneous Melanoma

The importance of skin cancer as an emerging public health dilemma is further underscored by the rising incidence and mortality attributed to cutaneous melanoma. Since 1950, reports document an increase of more than 600% in the annual incidence of cutaneous melanoma, with an attendant increase of 165% in annual mortality.\(^1\) Recent estimates from 2015 indicate that over 70,000 people have been diagnosed with melanoma in the United States, and almost 10,000 of them will die from their disease.\(^11\) It is reported that while melanoma only comprises of less than 3% of all skin cancers, it is considered responsible for nearly 70% of skin cancer mortalities.\(^14\) The lifetime incidence of melanoma among Caucasians in the United States is 2 to 3%,\(^15\) and ranks fifth in most common cancers among Caucasians.\(^16\) Unlike NMSC, cutaneous melanoma tends to afflict a younger population, making it the second leading cause of lost productive years and the most common cancer in women aged 20 to 29 years.\(^16\)

Cutaneous melanoma arises on the skin of the head and neck in up to 30% of cases, making it less common than NMSC in this
region. Nevertheless, the incidence of cutaneous melanoma of the head and neck remains greater than the relative proportion of total body surface area occupied by craniofacial structures, reflecting the relative impact of sun exposure and melanocyte density on the development of these lesions. The management of cutaneous melanoma provides an excellent example of the importance of a multidisciplinary team in head and neck oncology, as concerns for distant metastases predominate and because many lessons have been learned from the experience of melanoma in other anatomical sites.

**Note**
While melanoma only comprises of less than 3% of all skin cancers, it is considered responsible for nearly 70% of skin cancer mortalities.

### 23.2 Etiology

#### 23.2.1 Ultraviolet Light Exposure

Exposure to ultraviolet (UV) light has been identified as the main factor contributing to the development of melanoma and NMSC. The impact of early, intermittent, or excessive sun exposure and a history of blistering sunburns cannot be underestimated. The rising incidence of all types of skin cancer may be attributed to societal values on appearance and a tanned complexion arising from sunbathing or the use of artificial tanning beds, in addition to ozone depletion and increased surveillance. Potential links between artificial UVB exposure, such as in tanning beds, and skin cancer was investigated in the 1970s and found to increase the risk for melanoma by 15%, SCC by 125%, and BCC by 3% when compared to those who did not use artificial tanning beds. UVA exposure was initially thought to carry a lower risk of skin malignancy, but larger studies have disproved this finding due to the increased risk of melanoma. Chronic UV light exposure accentuates these acute effects and leads to the accumulation of mutated and dysregulated cells until SCC develops, further aided by activation of proto-oncogenes such as ras and inactivation of other tumor suppressor genes including P16 and INK4a/ARF. Mutations in the P16 tumor suppressor gene, alterations in the pathway of the protein sonic hedgehog, and abnormalities in the nuclear factor kappa B (NF-kB) signaling pathway have also been linked to the development of sporadic and familial cases of BCC.

The importance of genetics in cutaneous malignancy is epitomized by xeroderma pigmentosum, an autosomal recessive syndrome also suffer from NMSC at higher rates than does the general population. Congenital basal cell nevus syndrome, or Gorlin’s syndrome, is an autosomal dominant condition characterized by multiple pigmented BCCs, odontogenic keratocysts, rib anomalies, planter pits, and calcification of the falx cerebri. Basal cell nevus syndrome has been attributed to a loss of heterozygosity at chromosome 9q22–31, but the condition remains multigenic, with mutations, genetic polymorphisms, and environmental influences all contributing to its pathogenesis. Genetic abnormalities predisposing to skin cancer are not restricted to NMSC, however, as mutations are also associated with malignant melanoma.

#### 23.2.2 Molecular Biology and Genetics of Nonmelanoma Skin Cancer

The priority of sun exposure in the development of skin cancer of the head and neck is underscored by its effects at the cellular and ultrastructural level. UV light fosters DNA damage, inflammation, erythema, sunburns, and immunosuppression. Normally, following UV radiation, melanocytes produce melanin, which is stored in keratinocytes in the epidermal layer. Melanin serves to function as a barrier to hinder ultraviolet radiation from passing through to the deeper structures of the dermis. The synergistic effects of UVB (290–320 nm) and UVA (320–400 nm) radiation create mutations in keratinocyte DNA, often through pyrimidine dimer formation in the p53 tumor suppressor gene and through loss of the Fas-Fas ligand interaction. In the usual setting, these mutations are quickly repaired, but inadequate or failed DNA repair mechanisms, as in xeroderma pigmentosum, will allow clonal expansion of the mutated keratinocyte(s) that culminates in the development of cutaneous malignancy.

**Note**
The synergistic effects of UVA and UVB radiation induce mutations in keratinocyte DNA resulting in mutations in p53 suppressor and Fas-Fas ligand interaction.

**Note**
Both intense UV exposure resulting in blistering sunburns and chronic exposure are associated with increased risk of skin cancer.

#### 23.2.3 Molecular Biology and Genetics of Melanoma

Melanoma is thought to arise from a similar interplay of UV light-induced damage to melanocyte DNA, growth factor release, local immunosuppression, and escape from the controls of normal cell growth. Mutations in the melanocortin-1 receptor (MC1R) gene, cyclin-dependent kinase inhibitor 2a (CDKN2A), CDK4, NRAS, and BRAF have been linked to malignant melanoma, although aberrations in the latter two do not appear to be causative. These mutations are most often a result of...
extrinsic DNA damage, but it is estimated that 5 to 12% of melanoma is hereditary.27

Patients with familial melanoma have been shown to develop disease at a younger age than patients with sporadic melanoma, but there remains much debate over potential differences in biological behavior.28 Several clinical features have been associated with genetic susceptibility to melanoma: multiple cases of melanoma on the same side of the family, multiple primary cutaneous melanomas in the same individual, earlier age of onset of cutaneous melanoma, multiple nevi, and, possibly, other cancers.28 In the familial melanoma/dysplastic nevus syndrome (FM/DNS), a pattern of cutaneous melanoma arising in atypical moles has been identified in which the lifetime risk of melanoma for family members with dysplastic nevi approaches 100%. Through linkage analysis, this condition was mapped to chromosome 9p21 at the locus of the CDKN2A gene.17,26,29,30 Patients with inactivating mutations in CDKN2A have been reported to have a lifetime risk of melanoma of 50 to 90% by age 90.31 Unlike cutaneous SCC, abnormalities in p53 appear to play a less prominent role in the early stages of malignant melanoma.25

### 23.2.4 Precursor Lesions

Preexisting or precursor lesions play a prominent role in the development of both NMSC and cutaneous melanoma of the head and neck. Cutaneous SCC commonly arises from actinic keratosis (AKs), which are small, scaly lesions that appear pink, brown, or skin-colored. The presence of AKs imparts a cumulative lifetime risk of developing cutaneous SCC of 6 to 10%, and an individual lesion has an annual risk of progression to invasive cancer of 0.025 to 20%, depending on the duration of the lesion and the total number of AKs present.10 Cutaneous SCC has also been described to arise from Bowen's disease, bowenoid papulosis, and epidermodysplasia verruciformis. Similarly, at least 81% of patients with cutaneous melanoma describe a change in a preexisting lesion. Previous site of radiation, burns, scars, and chronic ulcerations have also been associated with increased risk of developing NMSC. It is currently thought that decreased E-cadherin levels in the local tissue favor the spread of atypical keratinocytes in perpendicular fashion through the dermis.32 Although the presence of numerous freckles or pigmented lesions places an individual at a higher risk of malignant melanoma, large congenital nevi, sporadic dysplastic nevi, and lentigo maligna have been noted to devolve to malignant melanoma at rates of 5 to 33%.17

### 23.2.5 Previous Skin Malignancy

Not surprisingly, a history of cutaneous cancer of the head and neck predisposes individuals to developing additional lesions, and there is a reasonable amount of crossover between NMSC and melanoma. Patients who have been treated for one BCC have a 3-year cumulative risk of developing another BCC of 40%, which is 10 times the risk of developing BCC for the general population. Similarly, patients with a history of cutaneous SCC have a 3-year relative risk of a second primary cutaneous SCC of 18%, which is 10 times the risk of initial lesions for the general population.31 According to SEER data, patients with a history of cutaneous melanoma are 10 times more likely to develop second primary melanomas than the rate of de novo melanoma in the overall SEER population.34

### 23.2.6 Other Risk Factors

Notwithstanding the importance of UV light exposure, there are several other patient, environmental, and genetic risk factors for the development of NMSC and melanoma. These associations are summarized in Table 23.1.

#### Radiation Exposure

The association between prior radiation treatment and the development of NMSC in survivors underscores the potential impact of ionizing radiation on skin cancer. A recent analysis of a cohort of childhood cancer survivors revealed that prior

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Table 23.1 Risk factors for developing skin cancer of the head and neck

<table>
<thead>
<tr>
<th>Melanoma and nonmelanotic skin cancer</th>
<th>Melanoma</th>
<th>Nonmelanotic skin cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood sun exposure</td>
<td>Family history of melanoma</td>
<td>Ionizing radiation, epidermodysplasia verruciformis, xeroderma pigmentosum</td>
</tr>
<tr>
<td>Intermittent sun exposure</td>
<td>Preexisting pigmented lesions</td>
<td>Actinic keratoses, immunosuppression, chronic lymphocytic leukemia, lymphoma</td>
</tr>
<tr>
<td>Severe sunburns</td>
<td>Large congenital nevi</td>
<td>Albinism</td>
</tr>
<tr>
<td>Fair complexion</td>
<td>Sporadic dysplastic nevi</td>
<td>Xeroderma pigmentosum</td>
</tr>
<tr>
<td>Blond or red hair</td>
<td>Lentigo maligna</td>
<td>Basal cell nevus syndrome, Bazex syndrome</td>
</tr>
<tr>
<td>Blue or green eyes</td>
<td></td>
<td>Chemical exposures, arsenic</td>
</tr>
<tr>
<td>Fitzpatrick class 1–2</td>
<td>Polycyclic hydrocarbons</td>
<td>Coal tar, psoralens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic irritation, burn scars</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior skin cancer (including melanoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bowen's disease, bowenoid papulosis</td>
</tr>
</tbody>
</table>
radiotherapy was associated with a 6.3-fold increased risk of developing NMSC, particularly BCC, and the majority of tumors occurred within radiation fields. Survivors were more likely to develop NMSC at a younger age than the general population, and NMSCs have emerged as the most common second malignancy to affect these individuals.\textsuperscript{35} Radiodermatitis frequently precedes radiation-induced SCC, and the rate of SCC metastases to the head and neck is 20\% higher in irradiated areas compared to areas that have not received radiation.\textsuperscript{36,37}

**Note**

Prior radiotherapy is associated with a 6.3-fold increased risk of developing nonmelanotic skin cancer, particularly BCC. The majority of tumors occur within radiation fields.

**Immune Compromise**

Immunosuppression, particularly in the setting of organ transplantation or hematologic malignancy such as chronic lymphocytic leukemia or lymphoma, constitutes another risk factor for developing cutaneous malignancies. Intensive immunosuppressive regimens for cardiac transplantation have been associated with aggressive cutaneous SCC and melanoma. Other solid organ transplants have also shown an increased risk for developing SCC. Following heart transplants in decreasing order, the lung, kidney, and liver show up to a 65-fold risk increasing in developing SCC while BCC shows an increase by 10-fold.\textsuperscript{38} In this population, cutaneous SCC occurs much more commonly than BCC, and local recurrence, nodal metastases, distant spread, and mortality occur more frequently.\textsuperscript{39}

**Note**

Immunosuppression for solid organ transplantation is associated with up to a 65-fold risk of developing nonmelanotic skin cancer.

**23.3 Histopathology**

**23.3.1 Basal Cell Carcinoma**

BCC exists in several histological subtypes: superficial, nodular, infiltrative, and micronodular. Typically, superficial BCCs (roughly 25\% of cases) tend to occur on the trunk and appear as plaque-like lesions, with well-defined borders. Nodular BCCs (60\%) present as the characteristic “rodent ulcer,” with raised edges around central ulceration, and they exhibit a predilection for the head and neck. Peripheral palisading is the histopathologic hallmark of these subtypes of BCC. Generally, superficial and nodular BCCs are not aggressive neoplasms, and they respond well to a variety of established techniques, including topical interventions.\textsuperscript{22,40}

**Aggressive Basal Cell Carcinoma**

Infiltrative, formerly known as morpheiform, and micronodular BCCs comprise only 2 to 5\% and 15\% of clinically detected BCCs, but they are regarded as more aggressive variants, with a tendency for local recurrence. Infiltrative lesions demonstrate a significant amount of subclinical spread, due to the existence of tumor islands and ill-defined projections. Micronodular lesions are aptly named due to their appearance as small nodules with peripheral palisading.\textsuperscript{22,40,41} Lesions have been described that demonstrate more than one histological pattern, and treatment is tailored to the more aggressive pathology. Aggressive BCCs have been defined as lesions with an initial diameter exceeding 1 cm, those that have recurred at least twice despite therapy otherwise deemed to be adequate, and extension into deeper, noncutaneous tissues.\textsuperscript{42} BCC rarely metastasizes, with reported incidences of fewer than 1\%, but it tends to be locally aggressive and can result in significant morbidity if neglected (\textsuperscript{\#} Fig. 23.1).

**Note**

Infiltrative lesions demonstrate a significant amount of subclinical spread, due to the existence of tumor islands and ill-defined projections.

**23.3.2 Squamous Cell Carcinoma**

The strong association between cutaneous SCC and UV light exposure predisposes SCC to appear on the head and neck. The lesions commonly appear as firm, pale to pink, textured lesions that may be hyperkeratotic. They frequently arise in the setting of a preexisting AK. Cutaneous SCC must be differentiated from AK and BCC, as well as keratoacanthoma, which is a rapidly growing ulceronodular lesion that resembles SCC histologically but can be differentiated by an experienced dermatopathologist and by its mercurial clinical course. Histological variants of SCC include verrucous carcinoma, spindle cell SCC, desmoplastic SCC, and basosquamous carcinoma.\textsuperscript{10}
Spindle Cell Squamous Carcinoma

Spindle cell carcinoma of the skin is an aggressive variant of SCC that is prone to perineural invasion, local recurrence, and regional metastases. Histologically, the hallmark spindle cells are poorly differentiated and surrounded by collagen. Diagnosis may be aided by electron microscopy and immunohistochemical staining for cytokeratins.

Desmoplastic Squamous Cell Carcinoma

Desmoplastic SCC is characterized by fine branches of tumor cells in the periphery and a desmoplastic reaction in the surrounding stroma. Desmoplastic cutaneous SCC demonstrates a predilection for arising on the ear, and it has been noted to be thicker and more advanced at diagnosis compared with typical SCC. These variants have been associated with 6 times the rate of metastasis and 10 times the rate of local recurrence as non-desmoplastic cutaneous SCC in a prospective series.

Basosquamous Carcinoma

Basosquamous carcinoma, also known as basaloid squamous (cell) carcinoma, is another aggressive variant of cutaneous SCC that is characterized by features of both SCC and BCC. Its key features include malignant basal cells with peripheral palisading nuclei and aggregates of squamous cells with eosinophilic cytoplasm without a transition zone between the basal cell and the squamous cell components. Although these lesions account for only 1 to 2% of skin cancers, they often demonstrate lymphatic and perineural invasion. Basosquamous carcinoma of the skin is characterized by local recurrence and metastasis, and adjuvant therapy may be indicated.

Note

Spindle cell carcinoma is prone to perineural invasion, local recurrence, and regional metastases.

Note

Basosquamous carcinoma of the skin is characterized by local recurrence and metastasis as a result of their affinity for perineural and lymphatic invasion.

23.3.3 Aggressive Nonmelanoma Skin Cancer

Both BCC and SCC of the skin can demonstrate clinically aggressive behavior in which lesions are prone to recurrence and metastasis, with attendant morbidity and mortality. These lesions are of particular importance to the head and neck surgeon, as aggressive NMSCs frequently fail standard treatments. The clinical and pathologic features of aggressive NMSCs are summarized in Table 23.2.

A large prospective study identified several factors on univariate analysis that were strongly associated with diminished disease-specific survival (DSS) in cutaneous SCC: recurrent lesions, invasion beyond the subcutaneous tissues, perineural invasion, and increasing depth of invasion. Based on statistical models, lesions larger than 4 cm, those with perineural invasion, and invasion beyond the subcutaneous tissues were associated with a decrease in DSS from 100 to 70% if one feature was present. Other histopathologic features that presage recurrence and metastases include the presence of inflammation and lymphovascular invasion. Fortunately, dermatopathologists now recognize the prognostic import of certain of the above features, and there is increasing documentation of important pathologic features, culminating in the ideal pathology report depicted in Table 23.3.

Note

Recurrent lesions, invasion beyond the subcutaneous tissues, perineural invasion, and increasing depth of invasion are all associated with a decreased disease-specific survival.

23.3.4 Merkel Cell Carcinoma

MCC was first described in 1972, and is considered to be an uncommon, clinically aggressive, neuroendocrine, skin malignancy associated with poor prognosis. Usually found on sun-exposed areas of the head and neck, the etiology is thought to include factors such as immunosuppression, UV damage, and viral factors. Nodal involvement has been shown to impact...
Carcinoma of the Skin of the Head, Face, and Neck

the 5-year survival in patients with microscopic involvement (42%) compared to a dismal 26% with clinically positive nodal burden. An independent staging system has been devised for MCC, reflecting its unique clinical behavior. Management for MCC remains best approached in a multidisciplinary fashion. The current standard remains wide local excision (WLE), with authors reporting 80% 5-year DSS with pathologically negative nodal status. It is thought that sentinel lymph node biopsy (SNLB) should be offered to patients undergoing WLE as 25 to 100% of patients without clinical evidence of nodal involvement may show microscopic involvement. Adjuvant radiation therapy (RT) following surgery, or for poor surgical candidates, is common secondary to MCC’s high rate of local and nodal metastases. Chemotherapy remains in debate as some authors report no survival benefit, while others have reported its use to be beneficial for recurrence and survival, especially those in the high-risk population.

Note
An independent staging system has been devised for MCC, reflecting its unique clinical behavior.

23.3.5 Cutaneous Angiosarcoma

Commonly presenting as a dusky, ill-defined, red-to-violaceous patch that tapers into normal-appearing skin, this malignancy tends to be aggressive in nature with an exceedingly low 5-year survival rate. An aggressive sarcoma with blood or lymphatic differentiation, this tumor is commonly found in the head and neck region, breast, and extremities. Some authors report certain characteristics that were associated with a poorer prognosis, namely tumor size greater than 5 cm, satellite lesions, and anatomical location (scalp compared to face). While chemotherapy use remains debatable for this disease, both surgery and RT seem to be the mainstay in therapy for this aggressive lesion.

23.3.6 Sebaceous Carcinoma

SC is a relatively rare tumor that commonly arises in the periorcular region, especially the upper eyelid, in patients older than 60 years. It can present as a painless yellowish-to-pink papule or nodule that may be confused for chalazion, blepharitis, or conjunctivitis. Treatment of SC relies on a multidisciplinary approach including surgery, chemotherapy, and RT. Muir-Torre syndrome should be considered in patients with SC, as internal malignancies may occur in conjunction with SC in this syndrome. Regional lymph node metastases occur between 17 and 30% of cases with a 5-year survival rate of 50%. Micrographic surgery (MMS) and WLE are the primary treatment options and regional metastases to the neck are addressed with neck dissection. RT is usually reserved for poor surgical candidates but commonly avoided secondary to the side effects of conjunctival keratinization. Topical mitomycin C has been tried for pagetoid invasion of the conjunctiva, while cryotherapy may also serve a role in epibulbar and pagetoid extension of SC.

23.3.7 Microcystic Adnexal Carcinoma

Microcystic adnexal carcinoma (MAC), also known as sclerosing duct carcinoma, is a rare, invasive facial malignancy with a predilection for perioral, periocular, perinasal, or scalp tissue. Perineural invasion is not uncommon, but metastases are rare. WLE has been associated with high rates of recurrence while MMS has reported 5 to 10% recurrence rates. Techniques tracking tumor extension have shown a mean defect four times the size of the initial lesion, so mapped scouting biopsies may serve as a good starting point for the initial stage of MMS.

23.3.8 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) most commonly occurs on the trunk and upper extremities but may also involve the head and neck. Rarely metastatic and considered to be a slow-growing dermal soft tissue sarcoma, DFSP may be locally destructive with irregular tentacle-like strands in its growth pattern that invades deeply and broadly. WLE or MMS are considered to be the mainstay of treatment for DFSP. Some authors support MMS for relatively small lesions in cosmetically sensitive areas to preserve cosmetic and functional outcome, but most patients are successfully treated with WLE. RT has also been shown to be beneficial for patients with recurrent lesions or those with positive margins.

23.3.9 Atypical Fibroxanthoma

Typically presenting as an ulcerated nodule on sun-damaged areas of the head and neck, this lesion is relatively easy to identify on frozen section as nonorganized, pleomorphic, spindle cells that can be associated with multinucleated giant cells. Atypical fibroxanthoma (AFX) is commonly found within the dermis but may extend into deeper tissues and cause local tissue destruction. Primary treatment consists of either WLE or MMS. Reported rates of recurrence for MMS range from 0 to 6%, while non-MMS surgery harbors a 9 to 16% reported rate.

23.3.10 Melanoma

Lentigo Maligna

Lentigo maligna has been described as an atypical proliferation of melanocytes within the epidermis, although it remains unclear if it is a precursor lesion to malignant melanoma. Lentigo maligna frequently occurs on sun-exposed areas of the body in older patients, reflecting the importance of chronic UV light exposure. Classically, the lesions arise on the cheek, with poorly defined borders and frequent subclinical extension. On histopathologic analysis, there is increased concentration of atypical melanocytes in the basal layer of the epidermis, appearing as single cells or junctional nests with underlying solar elastosis. Although lentigo maligna has not reached the point of invasion, it merits appropriate therapy because nearly 20% of lentigo maligna lesions may exhibit features of lentigo maligna melanoma.
Note
It remains unclear if lentigo maligna is a precursor lesion to malignant melanoma, however, 20% of lesions may exhibit features of lentigo maligna melanoma, so surgical excision is recommended.

Lentigo Maligna Melanoma

Although lentigo maligna melanoma is the least common type of melanoma (5–10% of cases), it presents a clinical challenge to head and neck surgeons because 50% of cutaneous malignant melanomas of the head and neck are lentigo maligna melanoma. Patients with lentigo maligna melanoma tend to be older, and these lesions are also commonly encountered on the cheek. Lentigo maligna melanoma is slowly progressive and exhibits a lengthy radial growth phase. The hallmark of lentigo maligna melanoma is invasion into the papillary dermis.

Superficial Spreading Melanoma

Generally regarded as the most common histological variant of melanoma, superficial spreading melanoma exhibits a radial growth phase that is followed by a vertical growth phase, heralding more aggressive disease. In superficial spreading melanoma, homogeneous neoplastic cells are distributed in all layers of the epidermis.

Desmoplastic Melanoma

Desmoplastic melanoma is an uncommon histological subtype that presents a unique clinical challenge because of its atypical appearance and aggressive behavior. The lesions may be nonpigmented and often occur on the head and neck, resembling NMSC as indurated and textured abnormalities. On histopathologic analysis, the lesions are poorly circumscribed, with infiltrates of spindle cells in a fibrous or myxoid stroma. Special staining for S-100 protein may be required for identification.

Clinically, desmoplastic melanoma is characterized by local recurrence, distant metastases, and a lower than expected risk of regional metastases. Perineurial invasion occurs frequently and has been linked to not only the high rate of local failure but also to distant metastases and diminished survival.

Other Variants of Melanoma

Nodular melanoma is characterized by an early vertical growth, leading to deeper lesions at presentation. Fortunately, nodular melanoma has been reported to comprise less than 15% of all melanoma lesions. Although it does not occur on the head and neck, acral lentiginous melanoma merits brief comment. It is encountered on the palms and soles and is marked by large, homogeneous malignant cells in the basal layer of the epidermis.

23.4 Diagnosis and Workup

23.4.1 History and Physical Examination

As in all conditions, an adequate history and physical examination holds the clues to the diagnosis in the majority of cases. Patients with risk factors such as fair skin, a history of early or severe sunburns, recreational or occupational exposure to UV light, family history of skin cancer, previous skin cancers, prior radiation treatment, and immunosuppression should undergo comprehensive cutaneous examinations on a regular basis, at least once per year. Early detection of skin cancer, regardless of histology, potentially allows less destructive treatments and promotes improved outcomes.

The most concerning complaint that suggests a diagnosis of skin cancer is growth or change in appearance of an existing cutaneous lesion. Other symptoms such as itching, formication, bleeding, ulceration, and pain may be the harbinger of aggressive disease. Vigilance, from both patient and provider, is required to follow skin lesions and detect significant changes over time. Individual memory and subjective assessment can be augmented by photographic documentation.

Note
The most concerning complaint that suggests a diagnosis of skin cancer is growth or change in appearance of an existing cutaneous lesion.

23.4.2 ABCDs of Melanoma

Following a simple ABCDE evaluation promotes recognition of suspicious lesions: asymmetry, border irregularities, color variation, diameter greater than 6 mm, and evolution of an existing lesion have been shown to correlate with malignancy, particularly melanoma. In addition to a thorough visual inspection of all cutaneous, lip, and mucosal surfaces, use of a Wood lamp has been shown to be useful in determining the true
clinical extension of pigmented lesions. By preferentially absorbing the UVA black light from the Wood lamp, the borders of pigmented lesions are depicted in greater contrast.70

Care must be taken when examining a patient with melanoma to determine if there are any surrounding abnormalities that could constitute satellite lesions. A comprehensive cutaneous examination should be performed to detect other suspicious lesions and signs of photoaging, including close inspection of the scalp. Dermoscopy, also referred to as epiluminescence microscopy, has also become an important noninvasive diagnostic tool for detecting melanoma, nonpigmented skin malignancies, and other dermatologic pathologies.73 A careful neurologic examination focusing on motor and sensory function of the cranial nerves should be performed to detect clinical evidence of perineural invasion, although most cases of perineural invasion are asymptomatic. Palpation of the parotid glands and cervical lymphatics should also be performed to detect regional metastases.

23.4.3 Biopsy

Once a suspicious lesion has been identified, a biopsy should be performed to determine the diagnosis. Although many techniques for cutaneous biopsy have been described, the method of choice must allow for an assessment of the depth. Excisional biopsy and incisional techniques such as punch biopsy, with a 2-, 4-, or 6-mm punch, are acceptable methods for lesions on the head and neck. If an excisional biopsy is performed, 1- to 2-mm margins should be taken, and the lesion should be marked and oriented to facilitate subsequent definitive excision, if necessary. If an incisional, or punch, technique is employed, biopsies should only be pursued in the setting of advanced disease. The resultant defect may be allowed to heal by secondary intention, or it may be sutured with absorbable material in either a linear or purse-string fashion. Shave or partial-thickness biopsies were previously thought to be inadequate because they provided no information on the depth of invasion.17 Although excisional biopsy is the currently recommended biopsy method for pigmented lesions by the American Academy of Dermatology, findings from Zager et al showed that a shave biopsy of melanoma was reliable and accurate in 97% of cases.74

23.4.4 Adjuncts

In the majority of cases of BCC and SCC, no additional diagnostic tests are necessary once the pathology has been confirmed. However, once an aggressive NMSC or melanoma has been diagnosed, additional tests may be performed to determine the extent of local disease or the presence of regional or distant metastases. In the setting of aggressive NMSCs, anatomical imaging may be indicated.

Imaging Studies

Evaluation of the extent of a clinically advanced lesion, potential bone involvement, and detection of nodal metastases may be accomplished with computed tomography (CT) scanning. Evidence of advanced perineural invasion may be manifest on CT scan images by enlargement of a neural foramen at the skull base, asymmetry in the pterygomaxillary space, or by asymmetric enhancement of a cranial nerve. Close attention should be paid to the parotid gland, the perifacial nodes, the external jugular chain nodes, and the upper cervical nodes, as these basins are commonly involved with metastatic cutaneous carcinoma.49

Because of its improved sensitivity with soft tissue, magnetic resonance imaging (MRI) is a useful adjunct in aggressive NMSC and melanoma, as it can detect perineural invasion, deep extension into subcutaneous tissues, and evidence of involvement of important sensory and neural structures, such as the orbital contents via gadolinium-enhanced MRI with fat suppression on a 3-Tesla scanners with high-field magnets.75 Both CT and MRI complement each other and together can provide reliable information for tumor staging and treatment planning. For instance, erosion of the calvarium may be detected on a CT scan, but a subsequent MRI will reveal the extent of bone invasion and indicate the presence and degree of intracranial involvement (Fig. 23.3). Other modalities such as ultrasound and positron emission tomography (PET) scanning, as well as emerging techniques that fuse anatomical and metabolic data, demonstrate great potential due to their noninvasive character, but their routine use remains unproved. Detection of systemic metastases in NMSC may be accomplished with simple laboratory tests including a liver panel and a chest radiograph, although this should only be pursued in the setting of advanced disease.

Guidelines for the detection of metastatic disease and follow-up of patients with cutaneous melanoma are determined by the clinical stage of the primary lesion. Algorithms have been developed that are widely accepted and may be obtained from the National Comprehensive Cancer Network (NCCN; www.nccn.gov) and the National Cancer Institute (NCI; www.nci.nih.gov). Patients with lentigo maligna melanoma and those with thin lesions with favorable signs (no ulceration, no extension to the reticular dermis) classified as stage 0 and stage IA do not require additional testing.

In early-stage melanoma, the recommended workup includes a lactate dehydrogenase (LDH) level and a chest radiograph (CXR). These two tests provide the foundation for the workup of a patient with all other stages of cutaneous melanoma, unless
there is clinical evidence of metastatic disease. In 2015, Fang et al showed that serum C-reactive protein (CRP) levels greater than or equal to 10 mg/L were associated with poorer overall survival in patients with any-stage melanoma, poorer disease-free survival in those with stage I/II disease, and can also be utilized to monitor disease progression. Although there is much interest in PET scan and fusion studies in the initial staging of melanoma, PET scans have not yet been proved to significantly alter the clinical course of patients with early-stage disease, and routine use of PET scans in the initial workup of patients with cutaneous melanoma remains under investigation.

Staging guidelines of melanoma of the head and neck has similarly evolved with the eighth edition (AJCC), with the inclusion of a thickness cutoff value for T1b melanomas rather than incorporating the previously accepted mitotic rate. As the AJCC continues to revise their criteria for staging purposes, treatment options continue to incorporate contemporary techniques and provide reliable information on the risk of metastasis and disease-specific mortality.

### 23.5 Staging

Accurate clinical staging of head and neck skin cancer is an essential part of treatment planning, and it provides useful, but generalized, prognostic information for both the patient and providers. The staging systems proposed by the American Joint Committee on Cancer (AJCC) are designed for use in primary lesions arising on all cutaneous surfaces. Updates to the 2017 AJCC guidelines for cutaneous squamous cell carcinoma (CSCC) have been perceived as marked improvement over earlier versions. Guidelines from the 2017 revision additionally mention specific factors including tumor thickness, anatomical site, perineural invasion, poor histological patterns, extension to bony structures, immunosuppression, lifestyle factors, and tobacco use associated with higher rates of local recurrence, poorer outcomes and prognosis, and increased nodal metastasis. Additional staging systems have been proposed prior to the eighth edition specifically evaluating risk factors as prognostic indicators not previously included in the seventh edition of the AJCC revision such as the immunosuppression, treatment, extranodal spread, and margin status (ITEM) prognostic score, and the staging system proposed by Brougham et al and Jambusaria-Pahlajani et al.

Staging guidelines of melanoma of the head and neck has similarly evolved with the eighth edition (AJCC), with the inclusion of a thickness cutoff value for T1b melanomas rather than incorporating the previously accepted mitotic rate. As the AJCC continues to revise their criteria for staging purposes, treatment options continue to incorporate contemporary techniques and provide reliable information on the risk of metastasis and disease-specific mortality.

### 23.5.1 Staging of Nonmelanoma Skin Cancer

The current AJCC staging system for NMSC, specifically CSCC is delineated in Table 23.4 and Table 23.5. Factors that are deemed as “high risk” include primary anatomical site ear, hair-bearing lip, greater than 2-mm depth, Clark’s level greater than or equal to IV, or perineural invasion. Implementing these “high-risk features” not only affects the staging of these lesions, but also directly allows for the better physical description of the lesion’s qualities. Clinical staging alone may be insufficient, and there is growing interest in detailed histopathology reports that contain more detailed information, as advocated by recent European guidelines (Table 23.3). Enhanced specificity from biopsies may be used to intensify the workup and treatment plan for high-risk lesions.

### Table 23.4 Clinical staging of cutaneous squamous cell carcinoma of the head and neck for primary tumors

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≥ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor ≥ 2 cm in greatest dimension, but &lt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor ≥ 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with cortical bone/marrow, skull base invasion and/or skull base foramen invasion</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor with gross cortical bone/marrow invasion</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor with skull base invasion and/or skull base foramen involvement</td>
</tr>
</tbody>
</table>

Source: Adapted from the 2017 American Joint Committee on Cancer System.
The Challenge of Regional Disease in Nonmelanoma Skin Cancer

Until the most recent AJCC updates, a patient could have a small, isolated parotid metastasis or extensive involvement of the parotid and cervical lymphatics and be considered to have N1 disease—this discrepancy has been addressed but continues to evolve. Previously, O’Brien and colleagues touted a modified staging system (Table 23.6) that has since been revised by Forest et al to not only include the parotid as part of the staging, but also to stratify the lesion by size in addition to cervical lymph node size and number as updated in the previous 2010 AJCC guidelines.88 Although O’Brien and colleagues’ work originally reflected the expansion of the 2002 AJCC guidelines, Forest et al further based their revision on the 2010 updated guidelines, which also incorporates subgroups of lymph node number and size further stratifying the parotid into three subgroups dependent on the lesion being under 3 cm (P1), 3 to 6 cm/multiple nodal disease (P2), or nodes greater than 6 cm/facial nerve or skull base involvement (P3). This was further revised to group both the parotid and cervical nodes and stratify based on the size and number of nodes, now known as the N1S3 system (2013). This system simplified O’Brien’s staging system by classifying patients into three groups or stages: (I) single lymph node less than 3 cm; (II) single lymph node greater than 3 cm or multiple nodes less than 3 cm; and (III) multiple nodes with maximum diameter greater than 3 cm. Results from this classification showed that stages I, II, and III were found to have a 90, 75, and 42% disease-specific survival at 5 years, respectively. Postoperative RT and histological presence of extracapsular spread were also found to be independent predictors of disease-specific survival.88

23.5.2 Staging of Melanoma

Staging in melanoma has been subjected to intense and continuous scrutiny and constitutes a reliable tool. Although the clinical features used to predict prognosis in cutaneous melanoma have matured, early efforts to stratify risk by location of the lesion and depth of invasion have been substantiated by subsequent work. For instance, lesions arising on the head and neck have been shown to have higher rates of recurrence and lower survival rates than lesions on other anatomical areas.79 Among head and neck melanomas, patients with lesions arising on the scalp and in the temporal area have worse survival rates than patients with lesions of other subsites.80 Perhaps the most compelling work into the prognostic features of cutaneous melanoma was performed by Clark and by Breslow, who correlated the depth of invasion or thickness of cutaneous melanoma with biological behavior, respectively.81,82 Their complementary work originally reflected the depth of invasion or thickness cutaneous melanoma with the most powerful independent predictor being tumor thickness.83 With the recent 2017 eighth edition guidelines, mitotic rate was replaced with more specific thickness cutoff value of 0.8 mm in T1 lesions as it showed a stronger association with outcome in comparison to the previously measured mitotic rate.85

Table 23.5 Clinical staging of cutaneous squamous cell carcinoma of the head and neck for distant metastases

<table>
<thead>
<tr>
<th>Distant metastases (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Lymph node staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>TisN0M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3N0M0, T1N1M0, T2N1M0, T3N1M0</td>
</tr>
</tbody>
</table>

Note: Deep invasion defined as either beyond the subcutaneous fat or greater than 6 mm; perineural invasion for T3 classification defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliper, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.


The prognostic value of mitotic rate has been questioned; however, once measured, mitotic rate was the strongest independent predictor of survival among patients with cutaneous melanoma, with the strongest association with outcome in comparison to the previously measured mitotic rate.83 With the recent 2017 eighth edition guidelines, mitotic rate was replaced with more specific thickness cutoff value of 0.8 mm in T1 lesions as it showed a stronger association with outcome in comparison to the previously measured mitotic rate.85

Table 23.6 Clinical staging of cutaneous squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Regional lymph nodes (N) clinical N (cN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N2a</td>
</tr>
<tr>
<td>N2b</td>
</tr>
<tr>
<td>N2c</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td>N3a</td>
</tr>
<tr>
<td>N3b</td>
</tr>
</tbody>
</table>

Abbreviation: ENE, extranodal extension.

Note

Among head and neck melanomas, patients with lesions arising on the scalp and in the temporal area have worse survival rates than patients with lesions of other subsites.
2017 American Joint Committee on Cancer Staging System of Cutaneous Melanoma

The current staging system for cutaneous melanoma reflects a series of international collaborative efforts to accurately depict the biological behavior of the disease. The system incorporates clinical staging, which is determined by histological assessment of the primary lesion plus a clinical and radiographic assessment of metastases, and pathologic staging, which fuses histopathologic detail from both the primary lesion and regional nodes, as determined by sentinel lymph node biopsy (SLNB) or regional lymphadenectomy.84 The 2017 AJCC staging system for cutaneous melanoma and the stage groupings are listed in Table 23.7 and Table 23.8, respectively.85

Classification and Staging of Localized Melanoma

Staging for cutaneous melanoma is based on the TNM system, in which T represents the primary tumor, N depicts regional node metastases, and M indicates distant metastases. Tumor thickness and the presence (or absence) of ulceration comprise the key determinants of the T stage with the exception of T1b because of their strong and independent impact on prognosis. In the previous 2010 AJCC revision, mitotic rate greater than 1/mm² was found to serve as an important prognostic factor for a higher risk for metastasis. This histological criterion has now replaced the previous Clark's level grading and defines the subcategory of T1b lesions. For all thicker lesions, the Breslow thickness and the presence (or absence) of ulceration comprise the key determinants of the T stage with the exception of T1b because of their strong and independent impact on prognosis.

Patients with localized melanoma are classified as stage I or stage II, with various subclassifications, based on the tumor thickness, histological features of the primary lesion, and the absence of clinical, radiographic, or histopathologic evidence of metastases to the regional lymph nodes (as determined by SLNB) or other sites. Patients with stage I disease are presumed to have a low risk for metastases and mortality from melanoma; patients with stage II disease have an intermediate risk of additional disease-related morbidity or mortality. Stage II also includes patients with ulcerated lesions greater than 4-mm thick (T4b) without evidence of regional metastases from sentinel node biopsy, but the high-risk nature of these aggressive lesions is accentuated by its classification as stage IIC.

Classification and Staging of Regional Metastasis

The differences in the clinical and pathologic staging of cutaneous melanoma appear more obvious in the setting of regional metastasis. Patients found to have palpable or radiographic evidence of nodal metastases are classified clinically as stage III, but clinical staging fails to detect occult metastases. With the increasing use of SLNB, pathologic staging of the regional nodes can be performed. The status of the regional lymph nodes has emerged as the most powerful indicator of recurrence and survival, and the number of involved nodes, plus the disease burden within the nodes, exerts a significant impact on outcomes of patients with stage III melanoma.87,88 The number of involved nodes, the disease burden (microscopic vs. macroscopic or clinically detectable), the presence of ulceration in the primary lesion, and the presence of satellite or in-transit metastases are considered in both the N classification and the subcategories of stage III disease.89 Ulceration is the only feature of the primary lesion that alters the prognosis of patients with regional disease.

Note

Ulceration is the only feature of the primary lesion that alters the prognosis of patients with regional disease.
### Table 23.9 Staging of cutaneous melanoma

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Presence of in-transit, satellite, and/or microsatellite metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Melanoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 1 mm in thickness</td>
</tr>
<tr>
<td>a</td>
<td>&lt;0.8 mm without ulceration</td>
</tr>
<tr>
<td>b</td>
<td>&lt;0.8 mm with ulceration or 0.8–1 mm with or without ulceration</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 1–2 mm in thickness</td>
</tr>
<tr>
<td>a</td>
<td>1–2 mm without ulceration</td>
</tr>
<tr>
<td>b</td>
<td>1–2 mm with ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 2–4 mm thick in thickness</td>
</tr>
<tr>
<td>a</td>
<td>2–4 mm without ulceration</td>
</tr>
<tr>
<td>b</td>
<td>2–4 mm with ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor &gt; 4 mm in thickness</td>
</tr>
<tr>
<td>a</td>
<td>&gt;4 mm without ulceration</td>
</tr>
<tr>
<td>b</td>
<td>&gt;4 mm with ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Presence of in-transit, satellite, and/or microsatellite metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes not assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>One positive lymph node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes</td>
</tr>
<tr>
<td>a</td>
<td>One clinically occult (i.e., detected with SLNB)</td>
</tr>
<tr>
<td>b</td>
<td>One clinically detected</td>
</tr>
<tr>
<td>c</td>
<td>No regional lymph node disease</td>
</tr>
<tr>
<td>N2</td>
<td>Two or three positive lymph nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node</td>
</tr>
<tr>
<td>a</td>
<td>Two or three clinically occult (i.e., detected with SLNB)</td>
</tr>
<tr>
<td>b</td>
<td>Two or three, at least one which was clinically detected</td>
</tr>
<tr>
<td>c</td>
<td>One clinically occult or clinically detected</td>
</tr>
<tr>
<td>N3</td>
<td>Four or more positive nodes, or in-transit, satellite, and/or microsatellite metastases with two or more positive nodes, or any number of matted nodes with without in-transit, satellite, and/or microsatellite metastases</td>
</tr>
<tr>
<td>a</td>
<td>Four or more clinically occult (i.e., detected with SLNB)</td>
</tr>
<tr>
<td>b</td>
<td>Four or more, at least one of which was detected clinically, or presence of matted nodes</td>
</tr>
<tr>
<td>c</td>
<td>Two or more clinically occult or clinically detected and/or presence of matted nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastases (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>a</td>
<td>Distant metastasis to skin, soft tissue (muscle and/or nonregional lymph node). M1a (0)–LDH not elevated, M1a (1)–LDH elevated</td>
</tr>
<tr>
<td>b</td>
<td>Lung metastasis. M1b (0)–LDH not elevated, M1b (1)–LDH elevated</td>
</tr>
<tr>
<td>c</td>
<td>Distant metastasis to non-CNS visceral sites with/without M1a or M1b sites of disease. M1c (0)–LDH not elevated, M1c (1)–LDH elevated</td>
</tr>
<tr>
<td>d</td>
<td>Distant metastasis to CNS with/without M1a, M1b, or M1c sites of disease. M1d (0)–LDH normal, M1d (1)–LDH elevated</td>
</tr>
</tbody>
</table>

Abbreviations: LDH, lactate dehydrogenase; SLNB, sentinel lymph node biopsy.
Classification and Staging of Distant Metastasis

All patients with distant metastases are classified as having stage IV disease, but there remains some variability in the prognosis of patients with stage IV melanoma. Differences in the survival rates of patients with cutaneous, subcutaneous, distant lymph node, lung, and other visceral metastases prompted the AJCC to subdivide stage IV disease, with 1-year survival rates ranging from 40 to 60\%.[89] Detection of an elevated serum LDH, however, carries the poorest prognosis, signifying hepatic or osseous metastases, and its presence merits the M1c (1) or M1d (1) designation depending on whether there is involvement of central nervous system (CNS).[89,90]

Excluding the importance of LDH in staging, the search for serum biomarkers of prognosis, disease progression, or response to therapy continues. Several candidates have emerged: S-100B protein, CRP, tyrosinase, and loss of heterozygosity at tumor suppressor gene loci.[91] Although work into other biomarkers such as TA90 or TA90-IC is promising, continued investigation is required before the use of serum biomarkers becomes clinically applicable to detect metastatic or recurrent disease.[92] With the eighth edition AJCC updates, tumor-infiltrating lymphocytes (TILs) have also been proposed as a favorable prognostic factor, as studies have shown that they have been associated with less frequent SLN metastasis.

23.6 Treatment of the Primary Lesion

Diagnosis, staging, treatment of local disease, detection and treatment of regional disease, and prognosis are increasingly intertwined in the multidisciplinary treatment of aggressive NMSC and cutaneous melanoma of the head and neck. In the era of sentinel node biopsy, a procedure commonly performed coincident with extirpation of the primary lesion, important information is gathered that will further impact treatment and the patient’s prognosis. Although the diagnosis and treatment of primary and metastatic disease are separated in this chapter to simplify the discussion, one should remember that there is seamless overlap of these concepts in the clinical setting.

23.6.1 Treatment of Nonmelanoma Skin Cancer

Regardless of the treatment modality, more than 90\% of patients with cutaneous basal cell and SCCs have an excellent prognosis. Because of the high incidence and favorable response to initial therapy, these lesions are treated by a variety of providers, including family physicians, dermatologists, general surgeons, plastic surgeons, head and neck surgeons, and radiation oncologists. This diverse group of practitioners may choose from an equally diverse armamentarium to treat the majority of BCC and SCC of the head and neck: electrodissection and curettage, cryosurgery, wide local excision, Mohs’ micrographic surgery (MMS), photodynamic therapy, laser ablation or resection, RT, and certain topical agents. The challenge in NMSC lies not in eradication of the lesion but in determining in advance which lesions merit more aggressive or multidisciplinary treatment.

Cryotherapy

Cryotherapy has been a reliable method to remove AKs and low-risk NMSC. Cryotherapy involves cooling the lesion with liquid nitrogen, and it is readily performed in the clinic setting. Because general anesthesia is not required, cryotherapy remains a useful method in patients with bleeding diatheses or medical comorbidities that preclude general anesthesia; however, cryotherapy does not provide tissue for pathologic analysis, mandating that it be used with extreme caution in cutaneous malignancy. It is not indicated in cutaneous melanoma.[43]

Electrodissection and Curettage

In electrodissection and curettage, a technique commonly used by dermatologists, a curette is used to scrape the tumor from its bed, which is then cauterized. The process is repeated several times to optimize tumor removal. Although the curetted material may be sent for pathologic analysis, margin assessment is not performed. This technique should be used with caution in NMSC of the head and neck and is not indicated for melanoma.[43]

Wide Excision

Wide local excision has been the traditional standard for managing NMSC, and it remains integral to the treatment of aggressive NMSC. Wide excision of a lesion can be accomplished in a circumsferential or elliptical fashion without compromising the margins to facilitate reconstruction.

Surgical Margins

Discussion continues about the extent of resection and the required size of the lateral surgical margins, but one should always remember that the pathology and histopathologic features of the tumor ultimately dictate the margin size. Margins of 2 to 10 mm and 4 to 15 mm have been proffered for BCC and SCC, respectively. A recent prospective effort has determined that local control rates of 96 to 97\% can be achieved in BCC and SCC excised with a 4-mm margin, but the majority of these lesions were less than 20 mm in diameter.[93] Porceddu et al recently published minimal surgical margin recommendations on SCC and BCC lesions with or without high-risk factors, and recommends minimal margins for low-risk BCC to be 2 to 4 mm (≥98\% 3-year local control), and 4 to 10 mm in high-risk BCC lesions (90–95\% 3-year local control). The authors also found that low-risk SCC should have a minimal margin of 4 to 6 mm (80–95\% 3-year local control), while a high-risk SCC lesions should undergo a minimal margin of greater than or equal to 10 mm (60–80\% 3-year local control). Delineation between low-versus high-risk lesions included tumor size, T stage, tumor thickness, anatomical site, differentiation, subtype, perineural
Carcinoma of the Skin of the Head, Face, and Neck

invasion, rapid growth, borders, lymphovascular space involvement, margin status, immune status, chronic inflammation or scores, and previous RT.94

Note
The pathology and histopathologic features of the tumor ultimately dictate the appropriate margin size.

Although these recommendations for lateral surgical margin extent result in acceptable rates of local control, the histopathologic assessment of specimens after wide local excision comprises its greatest limitation. Traditional bread-loaf or four-quadrant sectioning techniques do not allow complete assessment of the peripheral margin, and tumor cells may be missed. Tumors with irregular shapes or significant subclinical spread may thereby escape excision, leading to local recurrence.95 By close collaboration with dermatopathologists, 360-degree margin assessment may be accomplished.

Temporal Bone and Skull Base Involvement

Certain situations demand more aggressive multidisciplinary treatment. Auricular and periauricular NMSCs exhibit a predilection for invading the temporal bone, often requiring sleeve, lateral, subtotal, or total temporal bone resection to achieve gross tumor clearance. Microscopically involved margins, nodal metastases, and perineural invasion are frequently encountered in these patients. Temporal bone invasion presages poor outcomes with overall survival of 63% at a mean follow-up of 26.7 months. Although the rarity of temporal invasion in NMSC precludes large prospective studies, adjuvant RT may lead to improved survival.96

Involve ment of the anterior skull base and calvarium also occurs in NMSC, although the true incidence is difficult to compute. The calvarium may be directly invaded by an overlying lesion (> Fig. 23.4) or it may be secondarily involved as tumor progresses centrifugally along embryonic fusion planes and cranial nerves or through the orbit. If the overlying tumor appears fixed to the pericranium, then bone invasion should be anticipated and appropriate imaging studies obtained. The vast majority of patients with calvarial or skull base invasion suffer from recurrent disease, and many have undergone numerous prior interventions, including radiotherapy. Nevertheless, craniofacial resection may be safely performed by a combined surgical team of head and neck surgeons, neurosurgeons, and reconstructive surgeons, with an acceptable complication rate. Patients requiring craniofacial resection have been shown to have 2-year survival rates of 76 and 92% for SCC and BCC, respectively. These patients benefit from adjuvant RT and, potentially, concomitant radiation and chemotherapy to maximize disease control and survival. Poorer outcomes are associated with intracranial extension, perineural invasion, and previous RT.97

Note
Patients who present with temporal bone involvement benefit from adjuvant RT and, potentially, concomitant radiation and chemotherapy to maximize disease control and survival.

Mohs’ Micrographic Surgery

First devised in the 1930s by a medical student named Frederic Mohs, this technique involves removal of cutaneous lesions in a staged fashion in the outpatient setting. Margins are processed with horizontal frozen sectioning, theoretically allowing assessment of 100% of the margin. Each specimen is marked and accurately oriented prior to processing, and residual tumor detected on frozen section is then mapped prior to focal reexcision. This process is repeated until margins are cleared. Full details of the surgical technique and processing methods may be found elsewhere.95

Although the process is labor intensive, excellent results have been reported in NMSC, with cure rates in primary BCC approaching 99%.98 Similar results have been noted in recurrent BCC, as well as in primary and recurrent SCC, but questions have arisen about its cost-effectiveness in the primary setting.99 MMS has demonstrated long-term control rates of 90% in selected, recurrent SCC.100 A cost analysis study conducted by Kavur and colleagues showed that MMS remained the lowest when compared to ambulatory surgery center (ASC) based surgery and hospital operating room based surgery with an average cost of $895.50, $1,698.52, and $4,188.17, respectively.101

Meticulous attention should be devoted to detecting the histopathologic features of aggressive NMSC—histology, degree of differentiation, perineural invasion, lymphovascular invasion,
invasion to the subcutaneous fat, depth of invasion, and inflammation. However, MMS is not indicated in patients with aggressive NMSC and deep invasion beyond the subcutaneous tissues. The presence of major neurovascular structures and the inadequacy of this technique for clearing tumor from bone, muscle, and salivary tissue complicate margin assessment and complete resection. Combining MMS with traditional radiation may be another surgical philosophy to maximize local control rates in aggressive or deeply invasive lesions. In aggressive NMSC, it should never be forgotten that multidisciplinary treatment is often required, and the Mohs’ surgeon should collaborate regularly with head and neck surgical oncologists, radiation oncologists, and medical oncologists.

**Radiation Therapy**

Since its introduction in the 20th century, RT has been a popular means of treating cutaneous malignancies, particularly for elderly patients, those deemed to be poor surgical candidates, and in cosmetically important areas such as the eyelids or nose. Although the various methods of radiation therapy are commonly grouped together for assessment, the use of radiation to manage NMSC entails a heterogeneous mix of techniques. Radiation therapy for NMSC includes external beam radiation with orthovoltage X-rays, megavoltage X-rays, electron beam, and interstitial therapy with cesium afterloading catheters. Similarly, delivery techniques continue to evolve, as plain film guidance and wedge pair techniques yield way to intensity-modulated radiation therapy (IMRT) and proton beam therapy. Radiation fractionation has evolved from split-course technique to altered fractionation with acceleration.

**Primary Radiation Therapy**

In general, radiation for cutaneous malignancy attempts to maximize the delivered dose at the skin surface while avoiding deeper structures, so the modern “skin-sparing” techniques used at other body sites are not applicable to cutaneous malignancies. Orthovoltage and electron beam techniques that have limited therapeutic range are the preferred modalities. Orthovoltage irradiation concentrates energies of 100 to 250 keV at the skin surface. The beam can be shaped by the use of relatively thin, custom-shaped lead cutouts, and intraocular shields can be used to protect the cornea. Because orthovoltage X-rays deliver energy in the diagnostic range that promotes an eightfold relative dose increase in bone compared with soft tissue, this technique must be used with caution in sites adjacent to, or overlying, bone or cartilage. Orthovoltage and appropriate energy electron beams are preferred on the scalp to minimize the risk of brain injury, but special mixed photon–electron “whole scalp” dosimetry setups and IMRT have emerged as viable alternatives due to improved-dose homogeneity at the planned tumor volume. Deeply invasive lesions and those lesions requiring treatment of the regional lymphatics require the use of higher-energy electrons, mixed beam electron–photon techniques, or IMRT. Typical cumulative doses range from 40 Gy for small primary lesions to 65 to 70 Gy for larger or recurrent tumors using a variety of fractionation regimens determined by the size and location of the lesion, as well as its proximity to dose-limiting adjacent structures.

Results from treating NMSC with RT are comparable with the methods previously discussed. Early BCCs respond well to external radiation therapy (XRT), with 5-year local control rates of 95%, but local control of larger or more advanced BCC or SCC falls to 56% in some series. Similar rates have been reported in the treatment of T4 SCC and BCC, with local control rates slightly higher than 50% in primary disease; local control may be expected in 80 to 90% of patients with T4 lesions after XRT and surgical salvage. However, in a randomized, prospective study of patients with BCC smaller than 4 cm, XRT was found to be significantly less effective than surgical resection in controlling local disease. Patients who underwent surgical management of their lesions were also found to have notably better cosmetic outcomes than did those treated with XRT, refuting the historical assertions of improved appearance with XRT.

Even in elderly patients or poor surgical candidates, treatment of NMSC with RT may not be a benign enterprise. Unless modern techniques are employed by experienced operators, the complication rate may be significant. These complications include cutaneous depigmentation, telangiectasia, scar contracture, lipodystrophy, necrosis of bone or soft tissue, atrophy, and ocular injury. Furthermore, the potential to induce a second skin cancer must be considered when making the decision to treat NMSC with XRT for young patients, because of the association between ionizing radiation exposure and the development of skin cancer.

**Adjuvant Radiation Therapy**

Despite the limitations and challenges of treating NMSC with primary XRT, adjuvant RT plays a significant role in the comprehensive management of aggressive lesions. Common indications for RT to the primary lesion after surgical extirpation include positive margins, advanced lesions, lesions located in the central H zone of the face, temporal bone or skull base involvement, and perineural invasion. Efforts to maximize local control may facilitate improved regional control if the clinically negative neck is radiated in the setting of high-risk primary lesions, but additional evidence is required.

**Photodynamic Therapy**

First introduced in the 1970s, photodynamic therapy (PDT) involves the administration of photosensitive drugs that are activated by light exposure, resulting in selective destruction of malignant cells. A variety of photosensitizing agents has been employed, including benzoporphyrin, 5-aminolevulinic acid,
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meta-tetrahydroxyphenoxychlorin (Foscan, Biolitec Pharma, Dublin, Ireland), and porphyrin sodium (Photofrin, Axcan Pharma, Quebec, Canada).\textsuperscript{112,113} PDT has been used as the sole treatment modality or in conjunction with surgical excision of recurrent or aggressive NMSC in elderly or infirm patients, achieving complete responses in 92\% of BCCs and 100\% of SCCs in a highly select population.\textsuperscript{113} Complications of PDT include delayed wound healing, discomfort, and increased sun sensitivity that persists 4 to 6 weeks after treatment, requiring protective clothing or sun avoidance.\textsuperscript{112,113}

**Note**

PDT may be best suited for the informed patient who is not able to tolerate surgery; however, effects such as delayed wound healing should be considered.

**Laser Ablation**

Although the laser is essentially another surgical tool that can be used to excise skin lesions, there are scattered reports of using the carbon dioxide \((CO_2)\) laser to ablate superficial NMSC. By using a \(CO_2\) laser in a fashion similar to laser skin resurfacing, local control has been achieved in roughly 97\% of superficial BCCs.\textsuperscript{114} Such applications of the laser, however, are limited by the same shortcomings of other ablative therapies—failure to assess and precisely control tumor margins.

**Topical Therapy**

The use of topical agents to treat superficial NMSC is increasing in popularity. Topical therapy appears to be useful in treating precursor lesions of NMSC, such as AK, and in managing superficial NMSC in older patients or in those who are not ideal surgical candidates. The most widely used agent is 5-fluorouracil, and it has been used with excellent success for AK.\textsuperscript{115} Imiquimod cream (Aldara, Graceway Pharmaceuticals, Bristol, Tennessee) is a topical immune response modifier that triggers cytokine and interferon release, increasing cell-mediated immunity.

Imiquimod has demonstrated clinical efficacy in eradicating AK, superficial BCC, Bowen’s disease (SCC in situ), extramammary Paget’s disease, cutaneous T-cell lymphoma, and the majority of nodular BCCs, although local control rates in nodular BCC are not as high as those in superficial BCC (65\% histological clearance vs. 87\% clearance).\textsuperscript{116,117} Although increasing the frequency of application may increase the response rate, there is an accompanying increase in application-site side effects such as discomfort and pruritus.\textsuperscript{117} Other medical interventions for NMSC include intraloesional injection of interferon \(\alpha\) (IFN-\(\alpha\)) and the application of retinoids, which appear to be more beneficial in preventing progression of premalignant conditions than in treating existing lesions.\textsuperscript{115}

**23.6.2 Treatment of Localized Melanoma**

**Excision**

Surgical excision remains the primary method for treating the primary lesion in cutaneous melanoma. Because of the aggressive behavior of cutaneous melanoma, historical surgical treatment involved wide margins; however, recent clinical trials have revealed that there is little difference in outcome between 3- and 5-cm margins and 1- and 2-cm margins, supporting the use of narrower margins in cutaneous melanoma.\textsuperscript{114,115} Most of these data are derived from other anatomical sites such as the trunk and extremities where larger margins are less problematic, but surgical margins of 1 to 2 cm are considered adequate in cutaneous melanoma of the head and neck, with the ultimate width determined by the thickness of the lesion.\textsuperscript{17} Lentigo maligna requires a 5- to 10-mm margin, and lesions less than 1 mm can be safely excised with a 1-cm margin.\textsuperscript{70} Intermediate-thickness lesions (1-4 mm) are typically resected with margins approaching 2 cm. Because of the poor prognosis associated with regional and distant metastases in melanomas thicker than 4 mm, local recurrence is less of a concern, rendering 2-cm margins adequate in these patients as well.

**Note**

Recent clinical trials have revealed that there is little difference in outcome between 3- and 5-cm margins and 1- and 2-cm margins, supporting the use of narrower margins in cutaneous melanoma.

**Mohs’ Micrographic Surgery**

Although debate persists about the reliability of frozen-section analysis of cutaneous melanoma, there is increasing interest within the dermatology community about the application of MMS to cutaneous melanoma. Discordance between en face frozen-section and permanent-section margin assessment has led dermatopathologists to counsel against the routine use of frozen sections in cutaneous melanoma.\textsuperscript{120} On the other hand, experienced dermatopathologists and Mohs’ surgeons have achieved 100\% sensitivity and 90\% specificity with frozen-section evaluation of margins in melanoma.\textsuperscript{121} Increasing sophistication in MMS and the use of rapid immunohistochemical stains has led to acceptable local control rates in melanoma in situ and lesions less than 0.75-mm thick, suggesting a notable incidence of subclinical disease in these early lesions. With final margins that rarely exceeded 1 cm but increased with tumor thickness, equivalent local control rates with MMS versus standard excision have been shown, but experience remains limited.\textsuperscript{120} Freeze artifact from MMS sectioning can alter the appearance of normal keratinocytes to resemble melanocytes making the task of diagnosis even more challenging for a dermatopathologist.\textsuperscript{122} A form of MMS, known as “slow Mohs,” involves a staged excision with rushed permanent sections, rather than frozen, followed by delayed reconstruction used commonly in lentigo maligna.

**Note**

Increasing sophistication in Mohs’ surgery and the use of rapid immunohistochemical stains have led to acceptable local control rates in melanoma in situ and lesions less than 0.75-mm thick.
Radiation Therapy

Despite the historical perception that melanoma is a radioreistant disease, radiation therapy is a viable component of the multidisciplinary armamentarium. Radiation therapy is frequently given in the adjuvant setting, but it has been used as the primary modality in select patients. Radiation therapy has achieved local control of 93% in patients with lentigo maligna and lentigo maligna melanoma when used as the primary treatment modality. Radiation therapy is currently used as the primary treatment modality only for patients with unresectable disease or for those deemed medically unfit for surgery.

Increasing the dose per fraction and decreasing the number of fractions has resulted in durable locoregional responses. Although some authors advocate the use of radiation therapy in elderly patients or anatomically challenging areas, the hypofractionated schedules should be avoided in proximity to neural or sensory tissues. Postoperative radiation therapy administered to 30 Gy in five fractions has resulted in 88% locoregional control in stages II and III melanoma, compared with nonirradiated historical controls who had locoregional failure rates of approximately 50%. Common indications include positive margins, recurrent disease at presentation, nodal metastases, perineural invasion, thick primary lesions, ulceration, satellite margins, recurrent disease at presentation, nodal metastases, approximately 50%.124,125 Common indications include positive margins, recurrent disease at presentation, nodal metastases, perineural invasion, thick primary lesions, ulceration, satellite margins, recurrent disease at presentation, nodal metastases, and nodal metastases who have not undergone sentinel node biopsy or regional dissection.

Increasing the dose per fraction and decreasing the number of fractions has resulted in durable locoregional responses.123 Although some authors advocate the use of radiation therapy in elderly patients or anatomically challenging areas, the hypofractionated schedules should be avoided in proximity to neural or sensory tissues.17 Postoperative radiation therapy administered to 30 Gy in five fractions has resulted in 88% locoregional control in stages II and III melanoma, compared with nonirradiated historical controls who had locoregional failure rates of approximately 50%.124,125 Common indications include positive margins, recurrent disease at presentation, nodal metastases, perineural invasion, thick primary lesions, ulceration, satellite margins, recurrent disease at presentation, nodal metastases, and nodal metastases who have not undergone sentinel node biopsy or regional dissection.

Other Techniques in Melanoma

As in NMSC, there are some medical options for the treatment of primary disease in cutaneous melanoma, although the indications are few. Systemic chemotherapy, primarily dacarbazine, has been utilized in advanced disease and in cutaneous metastases, with limited responses. The topical immune response modifier imiquimod and intralesional INF-α have demonstrated activity against lentigo maligna in anecdotal reports. There have been some attempts to eradicate lentigo maligna with cryotherapy and laser ablation, but the inability to accurately determine the margin status and a high recurrence rate has limited their applications. Although it is not recommended for the treatment of primary disease, CO2 laser ablation has been successful in the palliation of cutaneous melanoma metastases.

23.6.3 Reconstruction of Cutaneous Defects of the Head and Neck

Regardless of the histopathology of the lesion and the method used for its excision (i.e., wide excision vs. MMS), extirpation of head and neck skin cancer creates a defect with cosmetic and functional consequences. Like radiation therapy and chemotherapy, reconstructive surgery constitutes an integral component of the multidisciplinary treatment. Potential reconstructive options for an anticipated defect should therefore be considered during thorough surgical planning. Although cosmetic and functional concerns should never alter the oncologic sanctity of a resection, one should never forget that the primary goals in treating skin cancer of the head and neck are achieving the best patient outcome and eliminating disease.

23.7 Diagnosis and Treatment of Regional Disease

Regional metastases to parotid area and cervical lymph nodes indicate aggressive lesions and are associated with diminished disease control and survival in both NMSC and melanoma. Despite the shared predilection for nodal metastases in both NMSC and melanoma, the general management philosophies toward nodal metastases differ. Management of the neck in melanoma is a proactive endeavor, whereas treatment of regional disease in NMSC remains predominately reactive. Because the lymphatic drainage mechanisms and pathways are not specific to histology, techniques such as SLNB and molecular analysis of nodal specimens that are becoming commonplace in melanoma will be increasingly applied to aggressive NMSC.

Note

Regional metastases to parotid area and cervical lymph nodes indicate aggressive lesions and is associated with diminished disease control and survival.

23.7.1 Lymphatic Drainage Pathways

Unlike other anatomical regions, lymphatic drainage from cutaneous sites in the head and neck exhibits marked complexity and variability. In general, lesions anterior to a vertical line extending toward the vertex from the auricle will drain to the ipsilateral parotid gland and upper cervical lymph nodes, including lymph nodes along the external jugular chain. More posteriorly located lesions will drain to the postauricular, occipital, and posterior cervical nodes. Lesions in the midface and lower lip may drain to the bilateral anterior cervical nodes, including the superficially located perifacial nodes, submental nodes, and submandibular nodes. Lesions on the neck will likely drain to the closest underlying lymph nodes and those along the external jugular vein, but they are unlikely to involve the parotid gland. A simplified schematic of the lymphatic drainage for cutaneous sites in the head and neck is depicted in Fig. 23.5. Within this general framework, there is significant variability, as is evinced by studies that reveal a discordance of up to 34% between the clinical prediction and lymphoscintigraphy.

Note

While a general framework for lymphatic drainage is useful, a third of cases may demonstrate variability from the expected lymphatic drainage pathway.

23.7.2 Risk Factors for Regional Metastases

Nonmelanoma Skin Cancer

The reported rate of metastatic SCC of the skin ranges from 0.1 to 21% in the literature. The range of variance in the
literature is partly due secondary to the previously aforementioned issue that NMSC is not routinely reported by cancer registries or followed by SEER. Because of the relative infrequency with which regional metastases are encountered in NMSC, the metastases are generally treated after they are detected; however, patients with nodal metastases have been found to have diminished overall survival (46.7 vs. 75.7%), disease-free survival (40.9 vs. 65.2%), and disease-specific survival (58.2 vs. 91.5%) at 5 years compared with patients without nodal metastases.49 As a result, there is a growing appreciation that nodal metastases in NMSC demand aggressive treatment predicated on the early identification of high-risk features in the primary lesion or early detection of regional metastases through SLNB. Risk factors for nodal metastases in NMSC are summarized in Table 23.10.46,49,100,131 Increasing depth of invasion and the histological presence of lymphovascular invasion have exhibited the strongest correlation with nodal metastases.49

**Note**

Depth of invasion and the histological presence of lymphovascular invasion exhibit the strongest correlation with nodal metastases.

### Table 23.10 Clinical and pathologic stage groupings for cutaneous melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0M0</td>
<td>Tis N0M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1aN0M0</td>
<td>T1aN0M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1bN0M0</td>
<td>T1bN0M0</td>
</tr>
<tr>
<td>II A</td>
<td>T2aN0M0</td>
<td>T2aN0M0</td>
</tr>
<tr>
<td>II B</td>
<td>T2bN0M0</td>
<td>T2bN0M0</td>
</tr>
<tr>
<td>III A</td>
<td>T3aN0M0</td>
<td>T3aN0M0</td>
</tr>
<tr>
<td>III B</td>
<td>T3bN0M0</td>
<td>T3bN0M0</td>
</tr>
<tr>
<td>III C</td>
<td>T4aN0M0</td>
<td>T4aN0M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T N1–N3M0</td>
<td>Any T N3M0</td>
</tr>
</tbody>
</table>


### Melanoma

As in NMSC, the presence of nodal metastases in cutaneous melanoma portends a worse prognosis. Patients with subclinical lymphatic involvement detected on sentinel node biopsy have a 3-year disease-free survival of roughly 56%, compared with the patients with comparable primary lesions who have negative sentinel nodes and a 3-year disease-free survival of more than 88%. In fact, the presence of lymph node metastases has emerged as a stronger predictor of diminished disease-free survival and disease-specific survival than Clark’s level, Breslow thickness, and ulceration status.87

Much of the recent data on high-risk features for nodal metastases have been gleaned from prospective trials evaluating SLNB. Historically, the depth of the primary melanoma was the most significant determinant of regional metastases, as lesions less than 1-mm thick have less than a 5% rate of nodal metastases, and lesions greater than 4-mm thick have a 30 to 50% rate of nodal metastases.88,132 Additional risk factors for regional metastasis in head and neck melanoma are listed in Table 23.10.133 Erman et al found that a positive SLNB was the strongest factor for a decreased recurrence-free survival (RFS) and decreased overall survival (OS). Other factors such as an increased Breslow’s depth of the primary lesion and presence of ulceration were found to show a decreased RFS and OS, respectively.134 The Sunbelt Melanoma Trial is a large prospective randomized trial that evaluated the role of INF-α-2b therapy or completion of lymph node dissection for patients with SLNB-staged melanoma. The authors from this trial found no
survival benefit for adjuvant interferon therapy for patients with a single positive sentinel lymph node. In those patients with a negative sentinel lymph node (pathologically) but a positive lymph node (detected by reverse transcription–polymerase chain reaction [RT-PCR]), it was also found that there was no overall survival benefit for those who underwent completion lymph node dissections compared to those who underwent dissection in addition to interferon therapy.135

### Note

Cancers less than 1-mm thick have less than a 5% rate of nodal metastases, while tumors that extend more than 4 mm in depth have a 30 to 50% rate of nodal metastases.

#### 23.7.3 Treatment of the Clinically N0 Neck

Intervention in the clinically negative neck remains a highly debatable concept in NMSC, in contrast with the importance placed on histopathologic evaluation of lymph nodes in early- and intermediate-stage melanoma. The low rate of nodal metastases in NMSC, combined with a limited appreciation of the risk factors for nodal metastases and a historically conservative approach, has limited the meaningful evaluation of various techniques. As the incidence of NMSC continues to rise and the medical and surgical disciplines gain an improved understanding and appreciation of the risk factors and mechanisms of lymphatic spread, the management of the N0 neck will likely evolve. Because of the importance of histological assessment of the nodal basins in the staging and prognosis of cutaneous melanoma, the management of the N0 neck has matured through clinical investigation. Regardless of histology, the options for managing the clinically N0 neck in skin cancer of the head and neck include watchful waiting, elective neck dissection, SLNB, and elective radiation.

### Watchful Waiting

A conservative initial philosophy toward the parotid and cervical lymphatics has been the mainstay in the management of the clinically negative neck in NMSC. This is evinced by the retrospective nature of the numerous published reviews on parotid and cervical lymphatic metastases in NMSC. Conversely, expectant management of the neck in cutaneous melanoma has been reserved for stage IA lesions because of their negligible risk of nodal spread.88 Because of the valuable information obtained from assessment of lymph nodes in melanomas less than 4-mm thick and the perceived lack of clinical benefit for regional treatment in lesions greater than 4 mm thick, watchful waiting of the neck has been abandoned in intermediate-thickness melanoma.

### Note

Watchful waiting of the neck has been abandoned for intermediate-thickness melanoma.

### Elective Neck Dissection

The role of SNLB has widely replaced the elective neck dissection in the management of cutaneous head and neck melanoma. Although studies have shown improved rates of locoregional control with an elective neck dissection, no definitive improvement in survival benefit was observed leading to a strong proponents for observation of a clinically negative neck.136

There is little published literature on elective neck dissection in NMSC. Previous studies have shown histopathologic risk factors including recurrent lesions, lymphovascular invasion, perineural invasion, inflammation, poorly differentiated lesions, invasion beyond the subcutaneous fat, deeper lesions, depth greater than 4 mm, and lesions greater than 4 cm to be associated with lymphatic nodal involvement (► Table 23.10). These aforementioned factors may serve as the basis for those who advocate for elective treatment of the nodal basins. The pattern of nodal metastasis with the parotid gland serving as the primary echelon of the lymphatic has previously been described,137 and included in the management of cutaneous SCC of the head and neck secondary to the revisions proposed by O’Brien et al.138 Moore et al found in their series that 35% of the cases had isolated parotid metastases, while 42% of patients with parotid metastases also had occult spread to cervical nodal basins.89 These findings serve as the basis for including an elective neck dissection if the parotid gland is involved, and an elective parotidectomy if the cervical nodal bundle is involved (site dependent).

### Note

The role of SLNB has widely replaced the elective neck dissection in the management of cutaneous head and neck melanoma except in the cases of poor prognostic factors (► Table 23.10).

### Sentinel Lymph Node Biopsy

First introduced in 1992 by Morton et al, sentinel lymph node mapping and biopsy is predicated on the premise that metastasizing tumor cells will spread first to the draining lymphatic basin, and an identifiable node within that basin accurately represents the status of the entire basin.77 The role of SLNB has been well-documented in guiding the treatment for melanoma and breast cancer.138 Identification of a positive SLN has emerged as the most important prognostic factor for recurrence and survival in cutaneous melanoma.87 Conversely, there are little published data on the importance of SLNB in NMSC, but its potential is gaining acceptance.139,140 Schmitt et al have suggested that T2 tumors greater than 2 cm according to the AJCC-7 guidelines, and T2b tumors in the alternative staging guideline proposed by Jambusaria-Pahlajani et al (► Table 23.11 and ► Table 23.12) may warrant SLNB as they were found to have 11.9 and 29.4% positive SLNB findings, respectively.138 In cutaneous SCC, immunohistochemical staining and serial sectioning may identify metastatic deposits and increase the sentinel node positivity rate, which ranges from 7 to 22% in select patients as depicted in several systematic reviews and a recent prospective study.
According to current clinical practice, SLNB requires both preoperative lymphoscintigraphy and intraoperative lymphatic mapping. Preoperative lymphoscintigraphy involves the intradermal injection of 1 to 4 μCi of technetium-99m sulfur colloid or technetium-99m antimony trisulfide colloid in the four quadrants of the lesion periphery. Immediate and delayed images are then performed to identify the draining lymphatic basins. Intraoperatively, the radiolabeled dye may be augmented by the intradermal injection of isosulfan blue dye or methylene blue to increase the accuracy of the procedure. 

Evidence between the use of either agent alone is limited in head and neck literature but a case control study comparing the use of isosulfan blue compared to methylene blue tracer showed no significant difference in the success rate of sentinel node biopsy in those undergoing mapping for breast cancer. 

After obtaining baseline radioactivity levels with a gamma counter, the primary lesion is excised, and the previously identified basins are inspected with the gamma counter to locate areas of increased radioactivity. Small incisions are made over these areas, and each SLN is identified and removed based on increased radioactivity counts and bluish discoloration. Some authors routinely monitor the facial nerve in cases where the SLNs map to the parotid basin, although this is not a universal practice.

Identification of the SLN allows the detection of occult regional metastases, promotes accurate staging, and facilitates appropriate delivery of adjuvant therapies. Meticulous serial sectioning of the lymph nodes, augmented by routine analysis and immunohistochemical staining, has identified more patients with positive nodes than elective neck dissection.

Limiting formal neck dissections to those patients with positive sentinel nodes spares unnecessary surgical morbidity for the roughly 80% of patients with intermediate-thickness lesions who do not have regional metastases. Subsequently, systemic therapy, with its associated toxicities, may be targeted to those patients who are at the greatest risk of metastases.

Although SLNB has become well established in other anatomical sites, acceptance was gradual in the head and neck. Increasing experience with sentinel node biopsy in the head and neck has led to more widespread acceptance. Erman et al’s study reported that SLN status serves as a greater prognostic indicator over Breslow’s depth or ulceration in melanoma, further gaining credibility in management of cutaneous head and neck melanoma.

SLNB is commonly indicated for intermediate-thickness lesions from 0.8- to 4-mm thick, ulcerated lesions of any thickness less than 4 mm, and select patients with high-risk features in thinner melanomas, such as ulceration or mitotic rate.
greater than or equal to 1/mm². Because of the high presumed rate of regional metastases in melanoma thicker than 4 mm, there is no clear added benefit to sentinel node biopsy, but the data can be used to guide systemic therapy or place patients on clinical trials. This technique has been validated in head and neck cutaneous melanoma, with sentinel node identification rates exceeding 92%. Because lymphatic drainage in the head and neck may be highly variable, discordant drainage basins should be anticipated and investigated. SLNB in the head and neck remains challenging, because of the variability in lymphatic drainage, the proximity of the basins to the primary (which complicates differentiation of both radioactivity and color change between the primary and the nodal basin), and the higher number of sentinel nodes per basin.

In addition to these potential complications, some procedural and oncologic limitations of the technique have been proposed. Concerns about the potential increase in in-transit metastases from entrapped melanoma cells among patients undergoing SLNB have been refuted by subsequent reports.

Although there is an acknowledged learning curve for sentinel node biopsy, false-negative results have been documented in up to 10% of cases and have been attributed to surgical failure or insufficient histopathologic detection. By adhering to the "10% rule" proposed by McMasters and colleagues, detection of occult metastases may be optimized by removing all blue lymph nodes, all clinically suspicious nodes, and all nodes that are greater than or equal to 10% of the ex vivo radioactive count of the most radioactive sentinel node. A false-negative result may lead to delayed detection and treatment of regional metastases, which could negatively impact survival.

### 23.7.4 Horizons in the Detection of Regional Metastases

Using RT-PCR techniques to identify a battery of molecular markers of melanoma may increase the sensitivity of SLNB in detecting occult metastases. Potential markers include tyrosinase, MART1, Mage3, and gp100. Evolution of the laboratory techniques, such as electrophoresis-based PCR and PCR on previously paraffin-embedded specimens, may further increase sensitivity and accuracy in detecting micrometastases.

Additionally, identification of the events that promote lymphatic invasion and increased tumor vascularity may identify patients who would benefit from systemic treatment strategies, with potential markers of metastasis including NF-kB and activating transcription factor 2 (ATF-2).

The survival benefit of these advanced diagnostic techniques, as well as SLNB itself, remains debatable, and further investigation, or prolonged follow-up in ongoing studies, is required. In the absence of other minimally invasive tests with comparable sensitivity and specificity, lymphatic mapping and SLNB (or selective dissection), augmented by molecular diagnostics, comprise the best available means to assess the regional lymph nodes for occult metastases, provide reliable staging and prognostic information, and facilitate targeted application of comprehensive neck dissection, radiation therapy, and adjuvant therapy in cutaneous melanoma of the head and neck.

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**Table 23.12** High-risk features compared between 7th edition AJCC, ITEM, and alternative T staging proposed by Jambusaria-Pahlajami et al

<table>
<thead>
<tr>
<th>AJCC 7th edition CSCC tumor staging system high-risk features</th>
<th>The immunosuppression, treatment, extranodal spread, and margin status (ITEM) prognostic score</th>
<th>Alternative T-staging system proposed by Jambusaria-Pahlajami et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth &gt; 2 mm or Clark’s level ≥ 4, perineural invasion, location on the ear or lip, and poor differentiation</td>
<td>• Immunosuppression</td>
<td>T0—in situ SCC</td>
</tr>
<tr>
<td></td>
<td>• Treatment (surgery vs. surgery and radiotherapy)</td>
<td>T1—0 risk factor</td>
</tr>
<tr>
<td></td>
<td>• Extranodal spread</td>
<td>T2a—1 risk factor</td>
</tr>
<tr>
<td></td>
<td>• Margin status</td>
<td>T2b—2–3 risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3—4 risk factors or bone invasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tumor ≥ 2 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poorly differentiated histological characteristics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Perineural invasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tumor invasion beyond the subcutaneous fat (excluding bone invasion)</td>
</tr>
</tbody>
</table>

**Abbreviation:** CSCC, cutaneous squamous cell carcinoma.

**Note**

Sentinel lymph node status may serve as a more accurate prognostic factor than Breslow’s depth or ulceration in melanoma.
23.7.5 Management of the Positive Neck

Given the common drainage mechanism and pathways for cutaneous malignancies of the head and neck, the type of therapeutic neck dissection performed will be the same, regardless of pathology. Comprehensive neck dissection with preservation of vital neurovascular structures, when possible, is indicated for clinical nodal metastases or those detected by SLNB. The type of dissection performed must be tailored to the location of the primary and the metastatic focus and all intervening lymphatics addressed. In general, selective neck dissections may be performed if adjuvant radiotherapy is planned that will encompass undissected areas but modified radical neck dissections or comprehensive neck dissections of all at-risk levels should be executed when postoperative radiation is not an option.

Note

A selective neck dissection may be performed if adjuvant radiotherapy is planned that will encompass undissected areas, otherwise a modified radical neck dissection should be considered.

Multimodality Therapy of Neck Metastases

Nonmelanoma Skin Cancer

In both NMSC and melanoma, the clinical or histological detection of regional metastases demands aggressive treatment to maximize locoregional control and survival. Patients with lymphatic metastases from cutaneous SCC have demonstrated significant improvements in locoregional control (80 vs. 57%) and 5-year disease-free survival (74 vs. 54%) with surgery and radiation compared with neck dissection alone. Therefore, postoperative radiation therapy is recommended in patients with parotid or cervical metastases from NMSC after either comprehensive or therapeutic selective neck dissection. At-risk, undissected levels are included in the radiation portals, thereby minimizing potential surgical morbidity in levels with a low likelihood of involvement.

Extrapolating from the success of concomitant chemoradiotherapy in cervical metastases from SCC of the upper aerodigestive tract (UADT), patients with metastatic NMSC exhibiting high-risk features may benefit from postoperative concomitant chemotherapy and radiation therapy, extrapolating from experience with mucosal SCC and high-risk features. Although combined regimens lead to increased toxicity, concomitant chemoradiotherapy may be beneficial in aggressive and metastatic NMSC, but more evidence is required.

Melanoma

The administration of radiation therapy in metastatic cutaneous melanoma after comprehensive neck dissection has been shown to promote regional control of 94% at 10 years. Postoperative radiation therapy, delivered to 30 Gy in five fractions, is associated with 10-year disease-specific survival and distant metastasis-free survival of 48 and 43%, respectively, in patients with clinical stage III disease. Common indications for adjuvant radiation therapy include extracapsular spread, lymph nodes larger than 3 cm, multiple involved lymph nodes, recurrent disease, and less than radical or modified radical neck dissection.

Radiation Therapy as the Sole Means of Regional Treatment

In an effort to capitalize on the benefits of postoperative neck irradiation in metastatic cutaneous melanoma and to minimize the potential morbidity of parotidectomy or neck dissection, some authors have investigated the use of radiation therapy in the elective treatment of regional metastases. Using the hypofractionation schedule outlined previously, 5-year rates of local control, regional control, locoregional control, disease-specific survival, and disease-free survival of 94, 89, 86, 68, and 58%, respectively, were achieved with elective neck irradiation. Although there was not a formal control group, these rates were deemed to be better than historical controls, and elective neck irradiation has been proposed as an alternative in patients who are poor candidates for systemic adjuvant therapy or neck dissection. Because of its effectiveness in achieving regional control after removal of nodal metastases, radiation therapy may prove to be a reasonable alternative to SLNB or comprehensive neck dissection in patients with positive sentinel nodes, although additional study is needed.

Note

Elective neck irradiation may be considered as an alternative in patients who are poor candidates for systemic adjuvant therapy or neck dissection.

23.7.6 Management of the Unknown Primary with Neck Metastases

In both NMSC and melanoma, the development of regional metastases in the absence of a primary lesion presents a clinical challenge. Patients should be queried as to their history of skin cancer or skin lesions that have been removed previously. Often, an index lesion can be identified, but an exhaustive search for potential lesions should be undertaken in the absence of a clear history. Mucosal and ocular sources of metastatic melanoma should be investigated in melanoma of unknown primary. Importantly, patients with parotid or cervical involvement by SCC should be evaluated for primary lesions of the UADT.

Patients with regional metastases and no identifiable primary should be treated aggressively with neck dissection followed by XRT for NMSC. Concomitant chemotherapy may be beneficial in SCC with adverse features, as previously discussed. Patients with melanoma of unknown primary should undergo neck dissection, with the possibility of postoperative XRT to optimize regional control, and they should be evaluated for systemic therapy, as they have stage III disease. Although some authors have asserted that patients with only regional metastases from melanoma have improved outcomes compared with
patients with known primary lesions, additional studies have not demonstrated a difference in survival.166,167

Note
Patients with regional metastases secondary to a presumed nonmelanotic skin cancer and no identifiable primary should be treated aggressively with neck dissection followed by radiation therapy.

23.8 Treatment of Advanced and Systemic Disease

23.8.1 Nonmelanoma Skin Cancer

Because of the rarity of advanced or widely metastatic NMSC, very little data exist to guide its management. A few isolated case series demonstrate the potential benefit of decreasing tumor burden in patients with unresectable skin cancers, but no randomized studies exist to support the routine use of neoadjuvant chemotherapy in NMSC or to provide concise guidelines for systemic therapy.168,169 The success of newer, taxane- and platinum-based regimens in the treatment of SCC of the UADT, particularly the oropharynx and larynx, may be applied to disfiguring or otherwise unresectable NMSC of the head and neck.

At the present time, surgery with or without postoperative radiation therapy remains the mainstay for managing aggressive NMSC. The role of chemotherapy is predominately limited to concomitant therapy for high-risk regional metastases, distant metastases, and palliation; however, phase II studies have demonstrated overall responses and complete responses of 34 and 17%, respectively, in patients with locally advanced or metastatic NMSC with combinations of IFN-α, retinoic acid, and cisplatin. Although the results were better in patients with locally advanced rather than metastatic disease, the median response duration was 9 months, and the toxicities were deemed acceptable. The addition of cisplatin to an earlier regimen of IFN-α and retinoic acid appears to increase the efficacy of the combination.170,171 These results are promising, but novel approaches are needed in advanced, aggressive NMSC.

Note
Surgery with or without postoperative radiation therapy remains the mainstay for managing aggressive systemic nonmelanotic skin cancer.

Currently there are novel systemic agents in the pipeline for the treatment of locally advanced cutaneous SCC of the head and neck. The favorable toxicity profile of the epidermal growth factor receptor (EGFR) inhibitor showed favorable locoregional control in the treatment of mucosal SCC of the head and neck, which makes it an attractive candidate for those who cannot tolerate platinum-based therapy.172 Cetuximab, an EGFR inhibitor, has been used concomitantly with radiation therapy showing similar efficacy outcomes in a phase II trial. This trial, however, also showed that cetuximab concomitant to radiation therapy lowered compliance and had increased toxicity rates.173 Erlotinib, another EGFR tyrosine kinase inhibitor in combination with radiation therapy, is currently undergoing phase I trials in patients with advanced cutaneous SCC in the head and neck showing acceptable toxicity profiles.174 Other EGFR tyrosine kinase inhibitors, including panitumumab as a single agent, and neoadjuvant gefitinib are also undergoing phase II trials showing promising results in the treatment for cutaneous SCC of the head and neck.175,176 Agents targeting the programmed cell death 1 (PD-1) receptor, specifically pembrolizumab, are also showing meaningful antitumor activity while being well tolerated through a phase Ib trial.177 Systemic agents targeting the hedgehog signaling pathway have also shown promise in the treatment of metastatic basal cell carcinoma showing significant inhibitory activity.178 Vismodegib was approved by the FDA in 2012 for the treatment of advanced BCC. A phase II study with this agent demonstrated a response rate in 30% of patients with metastatic BCC and a 43% response rate in locally advanced BCC. This agent inhibits the smoothened pathway, which plays a critical role in the hedgehog pathway by increasing the level of tumorigenesis.179

23.8.2 Melanoma

Despite advances in the detection and treatment of primary melanoma, distant metastases will develop in roughly 30% of patients.180 Patients with stages IIB, IIC, and III melanoma are at high risk of systemic metastases and subsequent death. Treatment strategies have evolved to minimize the likelihood of distant metastases, but survival rates remain poor for patients who progress to stage IV disease.

Adjuvant Systemic Therapy for Advanced Unresectable Melanoma

As previously mentioned, only a few agents have been used over the last three decades for the treatment of advance-staged melanoma primarily consisting of stages III and IV disease. Although a 2013 Cochrane review demonstrated improvement in disease-free survival and overall survival with adjuvant high-dose IFN-α, selecting this agent, must be balanced with its known toxicity and decreased quality of life associated with this therapy.181

Nontargeted systemic therapy has previously been the mainstay treatment used to treat melanoma. Agents including temozolomide, platinum-based therapy, taxanes, vinca alkaloids, nitrosoureas, and tamoxifen have all been used with limited success. FDA-approved agent dacarbazine chemotherapy has been frequently used as a single agent, but partial response (PR) and complete response (CR) rates remain dismal at 15% (PR) and 5% (CR), respectively.182 Combination regimens with both cytotoxic and immunologic modulators, such as interleukin 2 (IL-2) or IFN-α–2b, were tried in the same study secondary to poor initial response rates, and the addition of interferon improved the response rates of dacarbazine, but survival duration was not significantly affected.182

Current research has focused therapy to target more specific regulatory pathways of melanoma. As discussed previously...
earlier in the chapter, agents that target specific pathways including cytotoxic T-lymphocyte-associated antigen (CTLA-4), PD-1 protein, inhibition of the BRAF oncogene, and live viruses which replicate and subsequently lyse tumor cells have shown promise. A CTLA-4 protein inhibitor, ipilimumab, has shown a 10 to 15% improvement in 3-year overall survival and was approved by the FDA in 2011. With studies estimating that 50% of melanomas harbor BRAF mutations, specifically the BRAF V600E mutation pathway, has shown promise with an overall improvement in progression-free survival and overall survival in those carrying the mutation. Agents that also target the PD-1 protein have shown promise in the treatment of metastatic melanoma. The PD-1 protein is involved with T-cell response within peripheral tissues, and its ligands are expressed in the tumor microenvironment. Two agents, pembrolizumab and nivolumab, are developed antibodies that target these ligands approved by the FDA in 2015. A CTLA-4 protein inhibitor, ipilimumab, has shown promise with improved response rates and a trend toward improvement in median overall survival. As molecular mechanisms and pathways are further studied, treatment for advanced melanoma continues to improve. As these newly approved agents are further studied, long-term outcomes and, most importantly, survival outcomes will dictate the treatment algorithm of the use of systemic agents for the treatment of melanoma.

### 23.9 Prevention

Common strategies to minimize sun and ultraviolet radiation exposure include wearing protective clothing while in direct sunlight, avoiding sun exposure during the midday hours, and wearing sunscreen. Epidemiologic studies have indicated that sunscreen use can result in a 10 to 15% decrease in skin cancer, potentially due to the limitations of early sunscreen formulations against UVA or to a sense of false confidence in skin cancer prevention. Failure to employ skin-protective behaviors has not improved survival in those carrying the mutation. Agents that also target the PD-1 protein have shown promise in the treatment of metastatic melanoma. The PD-1 protein is involved with T-cell response within peripheral tissues, and its ligands are expressed in the tumor microenvironment. Two agents, pembrolizumab and nivolumab, are developed antibodies that target these ligands approved by the FDA in 2015. Approvals for advanced melanoma continua to improve. As these newly approved agents are further studied, long-term outcomes and, most importantly, survival outcomes will dictate the treatment algorithm of the use of systemic agents for the treatment of melanoma.

### 23.10 Clinical Cases

#### 23.10.1 Case 1

Patient 1 is a 49-year-old man who underwent resection of an SCC of the left lower lip 1 year ago. He developed persistent swelling of the left lower lip that progressed to become an ulceronodular lesion.

#### Presentation

Patient 1 is a 49-year-old man who underwent resection of an SCC of the left lower lip 1 year ago. He developed persistent swelling of the left lower lip that progressed to become an ulceronodular lesion.

#### Physical Examination

There was a well-defined, ulceronodular lesion of the lower lip just to left of midline. The oral commissure was not involved, and there was no palpable lymphadenopathy. There were no cranial neuropathies.

#### Diagnosis and Workup

To obtain a tissue diagnosis, either an incisional biopsy of the lip mass (through the previous scar) or a fine-needle aspiration biopsy of the lip or neck mass could be performed. In this case, a 4-mm punch biopsy of the lesion was performed, in addition to a CT scan of the head and neck, from the skull base to the clavicles. Consultations were placed with reconstructive head and neck surgery, radiation oncology, and medical oncology because this patient with aggressive, recurrent SCC of the lip may require multidisciplinary care.

#### Options for Treatment

Although radiotherapy with or without chemotherapy may provide locoregional control in patients who are not reasonable surgical candidates, wide excision of the recurrent lesion in conjunction with either elective bilateral neck dissection or SLNB is reasonable, given his high risk of regional metastases. Radiation or concurrent postoperative chemoradiotherapy may also be indicated, given the recurrent nature of the neoplasm and the potential for adverse features.

#### Treatment of the Primary Lesion

WLE of the lower lip recurrence with 1.5-cm margins may be readily performed, with preservation of the oral commissure if possible. Immediate reconstruction was planned with...
Karapandzic flaps to maintain the continuity of the oral sphincter to maximize postoperative function (Fig. 23.8). Local and regional tissues provide the best color and texture match, with the potential to maintain innervation.

Treatment of the Regional Lymphatics
Because of the location and recurrent nature of this SCC, SLNB was performed. Preoperative lymphoscintigraphy mapped to bilateral level II lymph nodes, both of which were positive only on immunohistochemical staining. He subsequently underwent staged, bilateral selective neck dissections of levels I to IV.

Adjuvant Therapy
In the presence of a recurrent lesion, extracapsular spread in the two lymph nodes, multiple positive nodes, and perineural invasion, the patient required postoperative chemoradiation therapy. The primary bed and ipsilateral involved neck should receive at least 60 Gy, with 50 to 60 Gy delivered to the lower-risk contralateral neck and ipsilateral supraclavicular fossa via IMRT techniques. Based on experience in UADT SCC with aggressive features, there may be a role for postoperative concomitant chemotherapy and XRT in high-risk patients.

Summary of Treatment
For recurrent SCC of the head and neck with perineural invasion and regional metastases, aggressive multimodality therapy is required to maximize the chances for locoregional control. Local tissues provide the best match for facial defects, particularly in the lip so that a functional oral sphincter may be preserved. The presence of adverse histological features such as extracapsular spread and multiple positive nodes justifies the use of concomitant chemoradiation therapy, which has proved effectiveness in regional metastases of SCC of the UADT.

23.10.2 Case 2
A 3.5-mm melanoma of the posterior scalp.

Presentation
Patient 2 is a 38-year-old woman who noticed a rapidly growing pink nodule on the vertex of her scalp.

Physical Examination
On close inspection, there is 1-cm nodule on the vertex of her scalp. Palpation of the neck reveals no lesions.

Diagnosis and Workup
A punch biopsy of the lesion was performed, revealing a 3.5-mm-thick nodular melanoma invading to Clark’s level V, perineural invasion, but no lymphovascular invasion, regression, vertical growth phase, or satellitosis. She underwent a contrast CT scan of the head and neck, as well as a chest radiograph and an LDH level, all of which were normal. The lesion is therefore staged as T3aN0M0 (stage IIA) melanoma of the scalp.

Treatment of the Primary Lesion
Because the patient has no contraindications to surgery, she should undergo WLE of this lesion, with 1.5-cm margins. Although a variety of rotation flaps and scalp flaps are available for reconstruction, a split-thickness or full-thickness skin graft provides a reliable means of immediate reconstruction. Once the final margins are determined to be negative on permanent section analysis, a definitive reconstruction may be performed, although the benefits of such a procedure should be weighed against the patient’s overall prognosis.

Treatment of the Neck
Because of the risk of regional metastasis in this intermediate-thickness melanoma, this patient is a candidate for SLNB. After preoperative lymphoscintigraphy to localize the primary drainage basin(s), intraoperative lymphatic mapping followed by SLNB should be performed. In this patient’s case, the sentinel nodes mapped to the postauricular region, and two nodes exhibited microscopic foci of disease. Because of the involved nodes, she should undergo comprehensive posterolateral neck dissection (Fig. 23.9) and postoperative radiotherapy to the primary and neck to 30 Gy in five fractions twice weekly.

Adjuvant Therapy
After completing locoregional therapy, the patient requires close follow-up, according to the protocols established by the National Comprehensive Cancer Network (NCCN). The current 2016 NCCN guidelines recommend observation and only clinical trials with adjuvant therapy if available.

Summary of Treatment
This case outlines the routine management for intermediate-thickness melanoma, including WLE of the primary lesion with
Carcinoma of the Skin of the Head, Face, and Neck

Fig. 23.9 Superficial parotidectomy and comprehensive posterolateral neck dissection for micrometastatic melanoma of the vertex of the scalp. Note the comprehensive removal of all fibrofatty lymph node-bearing tissue of the occipital and postauricular region, as well as levels II to V and the superficial parotid specimen. Cranial nerve XI was preserved and is visible in the posterior triangle. Because of extensive dissection, postoperative physical therapy is mandatory in these patients to prevent shoulder syndrome.

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24 Scalp Reconstruction

Eric M. Genden

24.1 Introduction

Although seemingly straightforward, the reconstruction of the scalp has required creativity and innovation from surgeons throughout medical history. Creating a balance of appropriate coverage of underlying structures and maintaining cosmesis is oftentimes challenging. The range of defects can be of the scalp alone to deficits of the scalp, bone, and dura. Calvarial and scalp defects require managing potential cerebrospinal fluid (CSF) leaks in addition to contouring the skull aesthetically.1 Matching skin thickness and color as well as maintaining hair-bearing skin are goals of therapy that are not always attainable. Beyond trauma and congenital deformities, oncologic resection is a specific aspect of reconstruction that forces surgeons to be resourceful. Delays in treatment can lead to tumor progression and greater reconstructive complexity. Therefore, delaying resection to allow for tissue expansion is not often recommended.2,3 Scalp reconstruction should provide durable coverage, preserve blood supply, and allow proper wound drainage without breakdown and calvarial exposure.3 The challenge of patients with previous surgical scars, pre- and post-surgical radiation, and dural invasion requires much thought before treatment to fulfill these ideals.

The scalp can be a limiting factor in reconstruction. It is difficult to match in terms of thickness, color, and density of hair follicles. As a result, the best tissue type for scalp reconstruction is the scalp itself.1 Management historically focused on primary closure and the use of skin grafts to cover areas of granulation. Preservation of the pericranium allowed for better take of grafted skin. As early as the 1600s, calvarial perforation was suggested as a method of promoting granulation formation. The development of local flaps allowed for closure of defects and preserving hair formation and skin thickness. In the late 1960s and early 1970s, Orticochea4,5 described a four-flap and preserving hair formation and skin thickness. In the late 1970s, Lowsley6 described a three-flap technique for closing large scalp defects.

24.2 Relevant Anatomy

The scalp is composed of five distinct layers: skin, subcutaneous tissue, galea aponeurosis, loose areolar tissue, and the peristeum of the skull. The skin is the thickest compared with that on other areas of the body. The subcutaneous tissue contains most of the blood supply and lymphatics. The galea layer is the strength layer and provides the most limitation of scalp movement. It attaches to the fascia overlying the frontalis muscle anteriorly, the temporoparietal fascia laterally, and the occipital muscle fascia posteriorly. Deep sutures at this level help alleviate tension along the skin.6 Epicranial muscles lie between the loose areolar tissue and the galea.7 Mobility is greatest at the parietal regions of the scalp where the temporoparietal fascia overlies the temporalis fascia.1 Advancement from this area allows the most gain for rotational flaps. To help increase length, galeotomies can be used. Galeotomies at 1-cm intervals can decrease tension by 40% and gain 1.67 mm per incision.8 The cuts should be parallel to the blood supply to avoid devascularization, as the vessels are immediately superficial to the galea.6,9,10 Compromise of blood supply can lead to alopecia as well as necrosis of reconstructive flaps.10

The blood supply of the scalp is composed of branches of the internal and external carotid arteries. The anterior scalp receives its vascularization from the supraorbital and supratroclear arteries. The superficial temporal artery and the posterior auricular artery supply the scalp laterally and posterolaterally, respectively. The superficial temporal artery supplies the greatest region in the scalp and branches into frontal and parietal vessels.7 The posterior aspects of the scalp receive its blood supply from the occipital artery above the nuchal line. Below this area is supplied by the perforators of the trapezius and splenius capitis muscles. Collateralization between these distinct territories is extensive. The use of local flaps should incorporate one of these major vessel systems to ensure adequate vascularization. Venous drainage from the frontal, parietal, and occipital veins matches their corresponding arteries and drains the frontal, lateral, and posterior scalp into the external jugular vein.7

Neural innervation of the scalp is derived from a combination of cranial and cervical nerves. The anterior aspect is supplied by the first branch of the trigeminal nerve through the supraorbital and supratroclear nerves. Laterally, the zygomaticotemporal, auriculotemporal, and the lesser occipital nerves provide innervation from the second and third branches of the fifth cranial nerve. Along the posterior scalp, cervical branches from C2 and C3 provide branches for the lesser and greater occipital nerves. Superiorly, the scalp is supplied by the third occipital nerve and is a branch of C3. In general, the pericranium of the vertex of the skull is less sensitive than the inferior areas. Neither the bones nor the veins of the skull receive any proprioception or nociception.7

24.3 Classification of Defects

The size, depth, and location of the defect have the greatest impact as to what type of reconstruction should be used for scalp reconstruction. Although no one staging system exists, various algorithms have been suggested throughout the literature. Beasley et al11 describe a staging system based on size and suggest potential reconstruction options. Scalp defects less than 200 cm² are classified as stage IA. Stage IB defects are the same...
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size as stage IA, but they are associated with associated risk factors for failure, such as heavy trauma, infection, previous radiation, or a history of failed closure. Stage II defects are 200 to 600 cm² in size. Stage III defects are larger than 600 cm². Primary closure or local flaps are recommended only for stage IA defects, whereas free flaps are recommended for all other stages.11 Leedy et al11 differentiate defects by size and location. Anterior defects that are small and do not affect the hairline can be closed primarily. Rotational flaps are recommended to preserve or restore the hairline. Moderate (up to 25 cm²) and large defects (> 25 cm²) can be closed with rotational advancement flaps and temporoparietal flaps, respectively. Tissue expansion and Orticochea’s flaps are also useful. For larger parietal defects, tissue expansion is required. Skin grafting over muscle and rotational flaps are other viable options. For large occipital lesions, Orticochea’s flaps and tissue expansion are useful and rotational flaps are useful for smaller lesions that cannot be closed primarily. For vertex lesions, Leedy et al recommend primary closure for small lesions. For lesions less than 3 to 4 cm in width, closure with galeal scoring or a pinwheel flap is suggested. Otherwise, large rotational or advancement flaps with back grafting or tissue expansion are needed. Leedy et al recommend free tissue transfer for patients with near-total scalp defects. Ilbher et al2 reviewed defects from oncologic resections and created an algorithm for closure based on size and location. For defects less than 3 to 4 cm in size, primary closure is recommended. If the defect is less than 6 to 8 cm (4–5 cm near the hairline), a split-thickness skin graft or local flap is advocated. Defects less than 8 to 10 cm necessitate free flap closure. If the larger defect is occipital, regional flaps are potential candidates for reconstruction. Although opinions vary on when to use which reconstructive option, a thorough understanding of each is necessary before tailoring a treatment plan for an individual patient.

24.4 Options for Reconstruction

If primary closure cannot be achieved, even with the aid of galeotomies, several options are available to aid in reconstruction. Healing by secondary intention and allowing granulation of a defect is one method of closure. This technique requires meticulous care of the defect over several weeks of healing. However, it requires no additional surgery, does not require a vascular pedicle, and allows easy detection of tumor recurrence.12 This technique is useful in patients with multiple medical comorbidities that may impede wound healing. Split- or full-thickness skin grafting can be used over the granulation bed.

Skin grafting over the defect is another method of closure. It is helpful to graft over areas of granulation, intact pericranium, or muscle to allow for the greatest chance for the graft to take. Burring down the outer layers of the calvaria and revealing the diploic space can be useful to help with vascularization if the pericranium is not viable.2 The ideal areas to graft are nonirradiated defects with a good vascular bed and no need for postoperative radiation.3 Split-thickness skin grafts can cover a large wound area and allow for easy detection of tumor recurrence.1,12 Thinner grafts have a better chance of survival due to less nutritional requirements; however, they are not as durable as other modalities of closure. To improve graft survival on previously radiated bone that granulates slowly, galeal flaps can be used. These flaps rotate or transpose galea from sites adjacent to the defect and improve skin graft take by providing a vascular bed.11 Split grafts often are not cosmetically advantageous, with poor color and poor thickness matching. If meshing of the graft can be avoided, the appearance can be improved, but will sacrifice coverage surface area.

Tissue expanders follow the tenet of replacing scalp with and are useful in patients not limited by time constraints for reconstruction. As a result, the oncologic patient is not the best candidate for the weeks necessary to allow adequate expansion time.23 The process involves implanting an expander and inflating the device over several weeks. A fibrous capsule forms around the expander, allowing an increase in blood supply to the scalp.5 The expanders must be 2 to 2.5 times the size of the defect to be reconstructed.14 The shape of the expander can affect the amount of tissue gained. Round, crescentic, and rectangular expanders allow for 25, 32, and 38% tissue gain, respectively.15 Expanders are considered for planning of reconstruction or large defects of up to 50% of the scalp.16 The use of expanders enables maintaining the normal hair pattern by expanding the hair-bearing scalp. It is useful in tissue in which local flaps are inadequate secondary to the size of the defect, the trauma to tissue, or unacceptable alopecia or hairline distortion.2 Although the area of skin is increased with expansion, the number of hair follicles remains the same. As a result, the density of follicles is decreased the more the scalp is expanded.5 Complication rates can be higher than 20% and are more likely to occur in infected or irradiated tissue.3,13,17,18 Intraoperative rapid expansion allows a small increase in tissue gain by taking advantage of the mechanical creep of the tissue and with galeotomies may allow primary closure of larger defects of up to 5 cm at the vertex.10,14 External tissue expansion utilizes negative pressure on the scalp surface to increase the surface area for closure. External expander thickness ranges from 2 to 5 cm. The process takes 3 to 6 weeks and is associated with minimal risks.19

Local flaps transpose, advance, or rotate viable surrounding scalp into the defect for closure. They consist of skin, subcutaneous tissue, and galea. They enable closure of defects that cannot be managed with primary closure and provide excellent cosmesis. Combining the technique with skin grafting, the donor sites allow for better coverage in more cosmetic areas. Relocating hair-bearing skin to more visible areas increases the overall aesthetic appeal of this technique. Attempts at preserving the natural orientation of the hair follicles also should be made. Local flaps are useful in defects less than 6 to 8 cm in size away from the hairline and up to 5 cm near the hair border.2 The art of local tissue transfer requires experience and ingenuity for the surgeon to achieve acceptable closure and aesthetics. Various types of flaps can be utilized for closure of scalp defects and include yin-yang, pinwheel, Orticochea, V to Y, rhombic, Juri, and H flaps (Fig. 24.1, Fig. 24.2).1,2,4,5,6,20

Defects of the forehead and scalp are best managed as separate anatomical units to better preserve the hairline.5 If possible, local flaps should utilize a major arterial vessel to maintain axial blood supply.6 Minimizing tension at the skin with galea sutures reduces the risk of alopecia along the suture line. Avoiding devascularization and tension of rotational flaps is paramount to avoiding wound breakdown. Skin staples are also
helpful to avoid ischemia to hair follicles and can decrease inci-
sional alopecia.1 Dog ears that are formed during closure can be
left to resolve over time and eliminate the risk of compromising
blood supply during removal.16 The use of local flaps for large
defects is limited due to the size of the flap necessary for closure
as well as the inelasticity and lack of mobility of the scalp.21

Regional flaps for scalp reconstruction are useful for lower
occipital or temporal defects. The reach of these flaps is the
major limiting factor. Regional flaps are useful in palliative situ-
ations or in patients in whom longer procedures would be det-
ritimental to the patient.2 Temporoparietal, trapezius, latissimus
dorsi, and pectoralis major pedicled flaps are potentially useful
and provide coverage of 8 to 10 cm.2 The aesthetic match of
thickness and color is not ideal, and hair coverage is often inad-
equate; however, when the temporoparietal flap is used with a
skin graft, the result can be acceptable. In this approach, the
temporoparietal flap is raised and transferred into the defect
(▶ Fig. 24.3). The skin graft can then be harvested and applied
to the defect over the temporoparietal flap (▶ Fig. 24.4). The
long-term results demonstrate that the skin graft provides
excellent color match and tone (▶ Fig. 24.5).

Free tissue transfer has enabled the reconstruction of the
most complex defects. Near-total scalp defects, a history of
prior radiation, scarring from previous surgeries, and failure of
previous closure are difficult clinical dilemmas best closed with
free flap coverage.1,10,20 Hussussian and Reece11 noted 90% of
delayed free flap reconstruction was secondary to radiation
therapy. The use of bone with free flaps can aid in closure of cal-
varial defects, and watertight closure of the skin paddle allows
closure of dural defects when positioned appropriately.10 Free
tissue transfer can be limited in cosmesis secondary to thick-
ness and color matching difficulty as well as the lack of hair-
bearing skin. The superficial temporal as well as the occipital
vessels can be used for anastomosis.1,11,21 If these vessels are
not amenable, vessels in the neck are then explored. The length
of the pedicle can pose issues for reconstruction and interposed
vein grafts can be helpful in this situation.11,21 The latissimus
dorsi flap allows a large size, low donor-site morbidity, and
ease of harvest.22 The muscle has minimal bulk and a long
pedicle, and can be used with or without skin.2,3,10 Adding the
serratus anterior muscle allows for even greater scalp cover-
age.1 The largest scalp defects can be covered with two latissi-
mus dorsi free flaps. Rectus muscle flaps also allow large areas
to be covered with limited thickness. Adding a skin graft to lat-
issimus or rectus muscle eliminates a contour issue; however,
 flap monitoring, color matching/cosmesis, and durability of the
skin is decreased. The radial forearm is useful for smaller defects, and the anterior lateral thigh is another potential source in patients with limited flap bulk. Serratus anterior muscle and omentum can be used with skin grafts to gain coverage. The serratus flap can be harvested with vascularized rib to address calvarial defects. Parascapular fasciocutaneous flaps can be considered for reconstruction and offer a good thickness match to the scalp. The serratus flap can be harvested with vascularized rib to address calvarial defects.21,25 Parascapular fasciocutaneous flaps can be considered for reconstruction and offer a good thickness match to the scalp.23 Scapular flaps with skin offer a good substitute for forehead skin in terms of color, texture, and thickness. The length of surgery and recovery in older patients with multiple medical comorbidities can be a limiting factor in free flap reconstruction.23 Balancing patient body habitus, medical conditions, as well as the nature of the defect is necessary in determining the type of flap to be used.

Techniques such as hair transplantation can be used to improve aesthetics in patients after reconstruction. The results are the most successful if done as a second procedure and if follicular unit grafting is used. Success rates for hair implantation in free flaps are 90% and can be incorporated into split-thickness skin grafts. Calvarial defects add to the complexity of a scalp wound. Cranioplasty with the use of titanium mesh provides a solid, malleable, fixable framework, and can be used with methyl methacrylate; however, it can be subject to infection and extrusion. Tissues with radionecrosis or infection are more likely to have complications with alloplastic materials and may benefit from autologous tissue. Infected bone should be removed and cranioplasty delayed. Autologous split calvarial defects, split rib, and vascularized rib grafts are all potential reconstructive options. Chang et al recommend inclusion of myocutaneous free tissue for dural and calvarial defects to eliminate intractable dead space of the wound, decrease osteomyelitis risk, and aid in sealing off the surrounding tissue margin. Morbidity from cranioplasty is related to residual devascularized or infected bone in the wound, inadequate coverage with vascularized tissue, and the type of material used.

Artificial dermal grafts are another method of helping scalp healing. The outer layer is composed of silicon and provides mechanical protection and moisture modulations. The inner layer is a collagen–glycosaminoglycan matrix that provides a template for cellular growth. The artificial dermis is placed and the silicone layer is removed after 3 to 6 weeks, and a split-thickness skin graft can be placed. This process reduces operative time, donor-site morbidity, and hospital stay, as compared with flap reconstructions, and increases cosmesis and skin graft take with the regenerated tissue. However, a second surgical procedure is required and may not be as successful in patients needing or having completed radiation therapy. The reconstructive surgeon must be aware of potential pitfalls in scalp surgery. Patients who have undergone multiple resections and reconstructions have less tissue pliability and

Fig. 24.3 An extensive defect of the lateral scalp and forehead managed with a temporoparietal flap transferred into the defect.

Fig. 24.4 The skin graft is placed over the vascularized temporoparietal flap.
compromised vascularity of the scalp.\textsuperscript{2} Newman et al\textsuperscript{3} noted complications to be significantly higher in anterior scalp repair compared with other subsites. Thinner skin anteriorly provides less protection to bone or alloplastic materials and may contribute to this phenomenon. Contamination from the frontal sinus may also play a role in failure.\textsuperscript{3} Postoperative complications are more often encountered in patients with CSF leaks and in those undergoing adjuvant chemotherapy or radiation.\textsuperscript{3} Radiation to the scalp induces fibrosis and reduces elasticity. It is imperative to limit tension on the wound and preserve vascularity to decrease breakdown risk.\textsuperscript{1} The use of vascularized tissue is essential to provide durable and reliable results.

24.5 Conclusion

Scalp reconstruction can be achieved using a variety of options ranging from a skin graft to a regional flap to free tissue transfer. Determining the optimal approach to reconstruction is predicated on the defect size and the patient’s history of prior radiotherapy. A careful preoperative history and a discussion with the patient related to goals and expectations can help guide the surgical options. Extensive defects of the scalp continue to represent a challenge; however, free tissue transfer provides a dependable option.
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Fig. 24.8 The flap is used to reconstruct the defect, and the vascular anastomosis is performed with the facial vessels.

Fig. 24.9 Six-month follow-up demonstrates the well-healed wound.

References

Reconstruction of the Cheek and Face

25.1 Introduction

Reconstruction of the cheek and face presents unique challenges to the reconstructive surgeon where the aesthetic results are as important, if not more so, as restoring functional outcomes. The face plays a critical role in human interaction, self-identity, and recognition, and defects of the face can be very distressing for patients. The goal of reconstructive surgery is to restore form and function with like tissue if possible. Similarly, the basic tenet of following the “reconstructive ladder” should also be obeyed; however, in certain circumstances, advancing to a more complex means of reconstruction is indicated in order to achieve the most optimal results.

Tumors that involve the cheeks may also involve the nose, eyelids, lips, and ears by direct extension. While each of these areas poses unique reconstructive challenges and considerations that are deserving of their own chapter, we briefly discuss them here as they pertain to treatment of pathologies that arise primarily from the cheek area. Additionally, the cheek and face may be involved by outward spread of oral and maxillary malignancies and vice versa, and the reconstructive surgeon may be called upon to restore through-and-through defects. Finally, the facial nerve lies beneath the skin of the cheek and may need to be addressed when treating tumors of cheek that extend deeply or tumors of the parotid gland that extend superficially.

Note

The goal of reconstructive surgery is to restore form and function with like tissue if possible.

25.2 Relevant Anatomy

The cheek represents the largest component of the face. The boundaries include the preauricular sulcus along the tragus and root of the helix posteriorly, the zygomatic arch following the malar and lower eyelid junction superiorly, the lateral nasal sidewall and melolabial fold medially, and the lower border of the mandible inferiorly. Within this defined region that comprises the cheek, it is generally accepted that there are three aesthetic subunits: suborbital, preauricular, and buccomandibular. Some authors consider the skin over the zygoma separate from buccomandibular skin (= Fig. 25.1).

Placing incisions and therefore subsequent scars at the junction of the subunits results in more acceptable scars that will be less conspicuous as the scars will fall into natural shadows in the face. When the defect involves greater than half of the subunit, consideration to resecting and reconstructing the entire subunit is recommended, just as has been espoused for nasal subunit reconstruction by Burget and Menick. Consideration should also be paid towards aligning the incisions along lines of tension, so-called Langer’s lines. Incisions placed parallel to these lines are generally favorable resulting in finer scars compared to incisions that lie perpendicular to these lines.

After exiting the stylomastoid foramen, and giving off the posterior auricular branch, the facial nerve divides into two main trunks within the substance of the parotid gland. These are further divided into the five main branches of the facial nerve that supply motor innervation to the superficial muscles of facial expression: temporal, zygomatic, buccal, marginal mandibular, and cervical. Cheek skin malignancies may directly extend to the facial nerve, particularly as its branches exit the anterior border of the parotid gland, on the deep fascia of the masseter muscle, where they are only covered by superficial soft tissue.

The zygomatic, buccal, and cervical branches of the facial nerve are composed of multiple rami connected by internuncial branches, such that paresis resulting from transection of one of these branches is often incomplete and temporary. Excision or transection of the temporal branch, however, results in an inability to raise the eyebrow and brow ptosis in patients who are middle aged or older. During cheek surgery, this nerve is most frequently encountered over the zygoma. The marginal mandibular branch of the facial nerve is most superficial where it crosses the mandible anterior to the masseter muscle. Loss of this nerve may impair the ability to depress and evert the ipsilateral lower lip.

Cheek sensation is provided mainly by the terminal branches of all three divisions of the trigeminal nerve (V1, V2, and V3), whose branches often travel above the superficial musculoaponeurotic system (SMAS), just below subcutaneous fat. Though not debilitating, patients should be warned that permanent numbness might result from excision of cheek tissues.

The blood supply to the cheek is robust and includes the facial artery and superficial temporal artery, which communicate with each other via the transverse facial artery, running inferior to the zygomatic arch and superior to the parotid duct. There is collateral supply from the dorsal nasal artery, which is a terminal branch of the internal carotid artery, as well as the infraorbital artery, which is a terminal branch of the maxillary artery, a branch of the external carotid artery. The venous drainage system of the cheek is predominantly via the anterior facial vein, which subsequently communicates with the internal jugular vein, and the superficial temporal vein. Additional drainage via the infraorbital vein and deep facial veins that drain into pterygoid venous plexus and communicate with the cavernous sinus.

Finally, the parotid or Stensen duct arises from the convergence of the interlobular ducts of the parotid gland. It emerges along the lateral side of the masseter muscle and empties into
the oral cavity through a papillary opening across from the sec-
ond maxillary molar tooth. As it traverses the deep tissues of
the cheek, the parotid duct is surrounded by the buccal fat pad.
The parotid duct should either be reconstructed or ligated
when treating deep excisions of the cheek. If ligated, it is not
unusual for the patient to experience swelling and discomfort
that usually subside with time spontaneously.

Note
The parotid duct should either be reconstructed or ligated
when treating deep excisions of the cheek to prevent seroma
and infection.

25.3 Evaluation of the Cheek and
Face Defect and Determining the
Options for Reconstruction

The philosophy of the reconstructive ladder hinges on using the
simplest modality for closing a defect that will get the job done
satisfactorily. If a simpler technique cannot achieve an adequate
result, the reconstructive surgeon should proceed to the next
rung on the ladder and so forth until the defect can be closed
safely with acceptable results. All rungs of the reconstructive
ladder are applicable, including primary closure, skin grafts,
local and regional flaps, and free flaps. Key considerations are
the aesthetic result in terms of color, thickness, and texture
match. Equally important is to avoid distortion of adjacent facial
structures such as the eyelids, ear, and lips due to wound ten-
sion or late contracture. For this reason, local and regional flaps
as well as microvascular free flaps play a major role in all but
the smallest and most superficial of defects.

Often, disease processes that involve the cheek may also
extend to adjacent structures like the eyes, lips, or nose. In such
circumstances, it is critical to evaluate each defect independ-
ently, and reconstruction of the cheek should be performed
separately from these other facial structures. For example, a le-
sion of the cheek that crosses the nasal malar junction onto the
lateral nasal sidewall should ideally be reconstructed such that
the nasal defect is addressed independently of the cheek defect.

Note
Defects that involve more than one subunit should be
evaluated independently and reconstruction of each subunit
should be performed separately.

Tumors with deep extension may also involve other structures
such as the facial nerve, facial muscles, parotid duct, mandible,
maxilla, and buccal mucosa. Whenever possible, each of these
structures should also be addressed separately from cutaneous
cheek reconstruction.
25.4 Options for Management of Small Cheek Defects

25.4.1 Primary Closure

In most cases, the first rung on the reconstructive ladder is primary closure where the defect is closed directly with sutures (▶ Fig. 25.2). As mentioned, closure should take into account Langer’s lines in order to minimize tension on the closure that can result in widened scars and a suboptimal outcome. This oftentimes results in a very pleasing result; however, for larger defects, primary closure can distort adjacent structures and is not recommended. For example, closure of large defects in close proximity to the lower eyelid can predispose patients to an ectropion, and reconstruction needs to be tailored to address defects adjacent to these other structures. For practical purposes, primary closure is usually only applicable to defects less than 2 to 3 cm at most in its smallest dimension and, with closure, will not cross into another facial subunit.

**Note**

Closure of facial incisions should take into account Langer’s lines in order to minimize tension on the closure that can result in widened scars and a suboptimal outcome.

25.4.2 Local Flaps

Even though this represents a higher rung on the reconstructive ladder, using a local flap to reconstruct a small facial defect often supersedes using a skin graft in order to achieve a superior cosmetic result replacing “like with like.” A number of local flaps can be utilized in the facial and cheek area as with defects in other parts of the body such as transposition, rotation, V-Y advancement, or rhomboid flaps (▶ Fig. 25.3). Many of

![Fig. 25.2](a) Small cheek skin defects can be closed primarily in the direction of the relaxed skin tension lines after excision of Burrow’s triangles. (b) Note that the length of the wound increases substantially.

![Fig. 25.3](a) A rhomboid flap is a useful technique for reconstruction of the cheek without extending the scar to other facial structures such as the eyelid or lips. (b) The flap should be designed so that the tension created by transposition of the flap does not pull downward on the eyelids, causing an ectropion. (c) Postoperative appearance.
Reconstruction of the Cheek and Face

these local flaps are random pattern flaps where the blood supply to the flap is not directly identified. Care must be used when designing local flaps that the wound tension from flap rotation or advancement does not cause distortion of the eyelid(s) or mouth.

In contrast, there are also local flaps that are based on a known blood supply that can be used in order to reconstruct facial cheek defects. Pedicled flaps based on the superficial temporal vessels can be used with good results. The superficial temporal vessels can supply either a temporoparietal fascial flap that can be subsequently skin grafted, or a hair-bearing scalp flap. Note that if a scalp flap is used, the donor site defect can only be closed primarily if the width of the flap is kept to 3 cm or less. The temporalis muscle, based on the anterior and/or posterior deep temporal vessels, can also be used in combination with a skin graft to reconstruct cheek defects.

25.4.3 Moderate Defects

Moderate cutaneous defects of the cheek are best reconstructed with the cervicofacial flap (> Fig. 25.4). This flap is usually dependent on the patency of the facial artery to minimize risks of ischemia and necrosis to the margins of the flap. When the facial artery has been ligated, the flap may still survive based on collateral flow, but a delay procedure is recommended. The cervicofacial flap does depend on sufficient laxity in the face and jowls to provide sufficient tissue to reconstruct the defect. In certain circumstances, the flap can be extended onto the neck or even the chest in order to gain additional mobilization of the flap.

Surgical Technique and Considerations for Cervicofacial Flap

- The upper/superior incision is made from the superior margin of the defect and follows the upper border of the cheek subunit (e.g., orbital rim and zygomatic arch).
- The posterior border lies within the preauricular sulcus (i.e., the posterior border of the cheek subunit).
- A second lobe can be created postauricularly for especially wide defects. Otherwise, the incision is carried down to the neck.
- From the neck, the incision can be curved anteriorly, maintaining a broad base that includes the facial artery and vein. Alternately, for tall defects, the incision can be carried down to the chest, allowing for great superior movement (cervicothoracic flap).
- The plane of dissection is above the deep fascia (superficial musculoaponeurotic system, or SMAS, and parotid fascia).
- When the defect is extensive, the donor site for cervicofacial or cervicothoracic flap may require skin grafting.
- Several deep sutures should be used to suspend the flap to the zygomatic periosseum to prevent postoperative ectropion from developing.
- Closed suction drains are recommended to prevent seroma formation.

Others have described large pedicle flaps such as the pectoralis major myocutaneous flap and the supraclavicular flap for cheek defects. While they can certainly achieve the goal of resurfacing the neck and lower cheek, they are often limited in terms of reach for mid- to upper cheek defects.

25.5 Options for Management of Large Cheek Defects

25.5.1 Skin Grafts

In the setting that the wound cannot be closed primarily and locoregional tissues are inadequate, a skin graft may be a reasonable and viable option (> Fig. 25.5). For facial and cheek reconstruction, a full-thickness skin graft is recommended whenever possible as opposed to a split-thickness skin graft. A full-thickness graft will resist secondary contracture more than a split-thickness skin graft. While a simple and straightforward means of reconstructing cheek defects, the overall cosmetic result is often less than ideal with the use of skin grafts as there will always be discrepancy between the native facial skin and the skin graft. Additionally, skin grafts result in an especially poor reconstruction when the resection is deep and are not usable for through-and-through defects.

Note

For facial and cheek reconstruction, a full-thickness skin graft is recommended whenever possible as opposed to a split-thickness skin graft because the full-thickness graft experiences less contraction.

25.5.2 Microvascular Free Flaps

Unfortunately, in the treatment of malignancy, defects can be much more extensive than can be safely or effectively repaired using simpler methods. Furthermore, in patients who have had prior resections in the area or prior radiation therapy, the use of simpler modalities in the reconstructive ladder are fraught with high complication rates. Patients with exposure of vital structures such as the facial nerve, great vessels, underlying bone, or communication with the oral cavity necessitate more advanced and complex reconstruction in the form of a free tissue transfer (> Fig. 25.6).

Harvesting distant tissue to reconstruct the face adds a number of formidable challenges and considerations aside from flap design and performing the microvascular anastomosis. The use of distant tissue by definition incorporates “non-like tissue” to the face, which will always have a different texture, color, and hair growth pattern than the face. Despite these suboptimal contradictions to the tenets of facial reconstruction, acceptable functional and cosmetic outcomes can be achieved.

Note

The use of distant tissue flaps by definition incorporates “non-like tissue” to the face, which will always have a different texture, color, and hair growth pattern than the face.
Fig. 25.4 (a) The cervicofacial flap is useful for moderate-size cheek skin defects. (b) Here, a postauricular “lobe” is included in the design to help reach this very medial defect. However, many times a “uni-lobe” design is sufficient. (c) Deep sutures to the deep facial fascia minimizes ectropion by helping to suspend the flap. (d) Postoperative appearance after revision to remove standing cone (“dog-ear”) deformities.
Extensive oral cancers of the buccal mucosa can often erode through the external skin and result in challenging through-and-through full-thickness defects of the oral cavity and skin (Fig. 25.7). These defects mandate a free tissue transfer in order to close the oral cavity and also to resurface the facial defect. This can be achieved through a number of different modalities using a single free flap or, in more advanced defects, may even require two free flaps. When the reconstructive surgeon faces such defects, one must consider adequate recipient vessels and potential complications such as an orocutaneous or sinonasal cutaneous fistulae. Furthermore, in these settings, the need for radiation must also be considered and can have a significant detriment on the final aesthetic result and functional outcomes. In setting the anticipated postoperative radiation, we usually overcorrect flap volume and surface area by at least 10%.

Note

If postoperative radiation is anticipated, overcorrecting the flap volume and surface area by at least 10% will help preserve the optimal contour.

In certain circumstances, the overlying skin of the cheek is preserved and a volume deficit is created following resection of deeper tissues as occurs during a radical parotidectomy. Following such an extensive resection, oftentimes the great vessels as well as the facial nerve are exposed and would benefit from additional soft tissue coverage particularly in the setting of radiation. The use of a free flap is indicated not only to provide coverage of critical structures, but also serves to replace the volume deficit created following the resection. Simultaneous reconstruction of the facial nerve, if indicated, is discussed below.
Fig. 25.6 Large cheek skin defects that are deep (a), such as this one occurring following parotidectomy and skin resection with resulting facial nerve exposure (b), may benefit from a free flap reconstruction. (c) The anterolateral thigh (ALT) free flap is often a good match in terms of thickness to the cheek skin, although there can be a substantial color mismatch. (d) Postoperative appearance.
Fig. 25.7 (a, b) A through-and-through cheek defect can result from either the deep extension of a cheek tumor or superficial extension of a buccal or mandibular cancer, as in this case. (c) Many free flaps, such as the radial forearm free flap, can be designed with two skin paddles, allowing reconstruction of both the cheek and the buccal mucosa. Completed oral (d) and cheek (e) flap inset.
Reconstruction of the Cheek and Face

25.6 Lip Reconstruction

The lip subunit includes both the vermilion lip as well as the cutaneous lips bordered by the melolabial fold and nasal floor for the upper lip, and melolabial fold and mental crease for the lower lip.24,25 The lips should ideally be reconstructed separately with regard to function and appearance. Superficial, primarily cutaneous reconstructions of the lip and cheek at times may violate the subunit principle in some cases, sacrificing the aesthetic demarcation of the melolabial fold in order to spare the patient from multiple flaps.

Note

The lips should ideally be reconstructed separately from other facial subunits to preserve function and appearance.

V-shaped or W-shaped defects approaching a third of the lower lip and a quarter of the upper lip can usually be closed primarily, while slightly larger defects can be closed with unilateral or bilateral lip advancement flaps. Central defects approaching two-thirds of the lip width can be closed with an Abbe cross lip flap and lateral defects involving the oral commissure approaching two-thirds of the lip width can be closed with an Estlander cross lip flap. Blunting and medialization of the oral commissure is not uncommon with the Estlander cross lip flap but can be improved with secondary commissuroplasty.

The Karapandzic technique of creating circumoral neurovascular flaps is often the best method of maintaining the oral sphincter function in defects up to two-thirds of the lip or even slightly more. When the defect involves the commissure, a combination of an Estlander flap and a contralateral Karapandzic flap may be the best way of reconstructing the defect. Free flaps for mandibular and maxillary reconstruction may sometimes need to be combined with local flaps for lip reconstruction to give optimal results (see Chapters 10 and 6 on mandibular and maxillary reconstruction, respectively).

Note

Prior radiotherapy may impair the local tissue vascular supply and compromise the viability of random lip flap reconstruction.

Free flaps may be the best or only option for near-total or total lip reconstruction, particularly when such defects result from spread of a cheek tumor, leaving the cheek unavailable as a donor site. Free flap reconstructions are often suboptimal due to oral incompetence and skin color and texture mismatch.26,27,28 A folded fasciocutaneous free flap, such as the radial forearm flap, is used by many to restore a near-total or total lip defect. For the lower lip, the free flap is usually draped for a palmaris longus tendon graft that is suspended via bone-anchored sutures to the zygoma bones bilaterally. Such flaps act primarily as a “dam” in the lower lip that prevents drooling or a “drape” in the upper lip that prevents exposure of the maxillary teeth.

A common scenario in cheek- or buccal-based cancers is the creation of a through-and-through cheek defect with oral commissure involvement.29 With extensive involvement of the lip, there may not be adequate local tissues to reconstruct the lip and cheek separately without creating a very microstomotic oral aperture. In these cases, a folded fasciocutaneous free flap is utilized. The ALT flap, if not too bulky, is a good option for this reconstruction as there is usually enough skin laxity for primary donor site closure, and the pedicle usually gives rise to more than one cutaneous perforator, allowing for increased degree of freedom to tailor separate skin paddles for intraoral and extraoral surface reconstruction (► Fig. 25.8).

25.6.1 Surgical Technique and Considerations for ALT Flap Reconstruction of through-and-through Cheek and Oral Commissure Defects

• A thin, supple fasciocutaneous free flap, such as the ALT in most patients is preferred for restoration of through-and-through cheek combined with oral commissure defects (► Fig. 25.8). When the ALT is too bulky, a radial forearm flap, if the forearm is large enough, may be a reasonable substitute.
The exact dimensions of the intraoral and extraoral defects are measured. It is sometimes helpful to make a template out of paper or a sterile latex Esmarch bandage. Especially important is to restore the height of the upper and lower lips by making precise measurements and even slightly overcorrecting. When designing the ALT free flap, the distal portion of the flap is used for the intraoral lining and the proximal portion of the flap is used for the extraoral cover. This allows the distal portion to be inset first, deep into the oral cavity. If two perforators are not available, the two skin paddles can be left connected by a skin bridge along the lower lip, which is deepithelialized.

The cut edge between the two flaps becomes the new wet–dry border of the lip. Therefore, it is important for the width of the flap on the thigh to be long enough to account for both the lower lip height, plus the length of the wet–dry margin. The superior (proximal) margin of the ALT flap becomes the posterior margin of the extraoral cheek skin reconstruction, and the inferior (distal) margin of the ALT flap becomes the posterior margin of the intraoral buccal mucosal reconstruction. A few through-and-through quilting sutures, loosely tied, can eliminate dead space between the two flaps and recreate the appearance of a melolabial fold.

Fig. 25.8  (a) Some cheek defects will extend to the lips. (b) If possible, separate lip subunit reconstruction with local flaps is preferred. However, in the case of extensive (or recurrent) tumors, there may not be adequate local tissue for lip reconstruction without microstomia. (c) A two-skin paddle ALT flap based on separate cutaneous perforating blood vessel can be used to reconstruct both the buccal and cheek surfaces. (d) Completed reconstruction. (e, f) Postoperative appearance showing reasonable function.
25.7 Nasal Reconstruction

Defects of the nose are common following resection of cutaneous malignancies and may be an extension of cancers that start on the cheek or subunit regions of the face and vice versa. As with the lips, the ideal nasal reconstruction should be performed separately from reconstruction of other facial subunits. Nasal reconstruction begins with a careful assessment of the defect and the components that require reconstruction. Defects may be superficial, deep, or full thickness, and reconstruction may involve replacement of one, all, or a combination of external skin, structural support, and internal lining.

Aside from being a subunit of the face, the nose itself is further divided into nine subunits.29,30 The subunits are delineated by the natural contours and shadows of the nose. In the nose, more so than other regions of the face, the subunit principle dictates that defects involving more than half a subunit are best reconstructed by removing the remainder of the subunit and reconstructing the entire subunit.

Defects involving only the external skin can be reconstructed using a number of different modalities. Allowing a defect to heal secondarily often results in a poor cosmetic result as does a full-thickness skin graft, with the possible exception of the nasal dorsum. For patients not medically stable enough to undergo more complex reconstruction, these may represent potential alternatives to other more aesthetic, but complicated techniques. For most defects up to 1.5 cm in dimension, the use of local flaps often provides the best aesthetic result. A bilobe flap is ideally suited for reconstruction of defects of the lateral side wall or the nasal ala while a glabellar flap can recruit redundant tissue from the glabellar region for defects of the lateral nasal skin, structural support, and internal lining.

Complete alar defects can be reconstructed using a nasolabial flap based on a perforator arising from the facial artery; however, this approach often requires one or more revision operations in order to thin the flap and divide the pedicle to the flap.31,32 For more extensive soft tissue defects or defects involving the nasal tip, a paramedian forehead flap represents the best option for nasal resurfacing.33,34 The paramedian forehead flap is based on the supratrochlear vessels and requires secondary procedures in order to refine the reconstruction with flap thinning and for division of the pedicle.

When defects are full thickness or extend deeper than the external skin, structural support may be necessary in the form of cartilage grafts. Potential donor sites include septal cartilage, conchal cartilage, or rib cartilage grafts. When pre- or postoperative radiation is given, autologous cartilage is preferred because it does not undergo resorption to the degree that irradiated cadaveric cartilage does. Nasal lining can be replaced using local flaps from the nasal mucosa; however, for extensive defects of the nose or total rhinectomy defects, the use of microsurgical techniques may be needed.

Note

When pre- or postoperative radiation is given, autologous cartilage is preferred because it does not undergo resorption to the degree that irradiated cadaveric cartilage does.

25.8 Eyelid Reconstruction

Reconstruction of the eyelid represents another complex component of reconstruction of facial defects. The modality for eyelid reconstruction is, as always, dependent on the extent of the defect as well as the location of the defect.50,61,62 Repair of the upper or lower eyelid follows similar principles and replacing the missing anatomical layers that have been resected is necessary for lasting results, much as they are in nasal reconstruction.43 Using like tissue in general provides the most optimal outcomes and, therefore, local flaps and lid-sharing operations are preferred.

The eyelids are divided into an anterior lamella, composed of the skin and underlying orbicularis oculi muscle, and a posterior lamella, composed of the tarsal plate and conjunctiva. Defects involving only the anterior lamella can often be reconstructed using a full-thickness skin graft, harvested from the contralateral eyelid for the best color and texture match. For lower eyelid defects of the anterior lamella, a Tripier flap, which is an upper eyelid flap encompassing the anterior lamella of skin and muscle, can be harvested and mobilized to the lower eyelid to reconstruct the defect. The flap can be either a unipedicle or a bipedicle flap. If the posterior lamella is involved, then the tarsal plate and conjunctiva will need to be replaced and may require more complex reconstruction, including possible cartilage or mucosal grafts.

Full-thickness defects of the eyelid that are less than a third of the eyelid are best closed primarily using a wedge type closure paying careful attention to realign the lid margin. For defects that are larger than a third but less than half the eyelid, a local flap recruiting tissue from the lateral aspect of the orbit provides the most optimal means of reconstruction. The Tenzel flap is a flap that utilizes a lateral canthotomy in order to mobilize the redundant tissue of the lateral orbit into the upper or lower eyelid defect. The periorbital bone is included with this flap and remodels rapidly.

The use of thin fasciocutaneous flaps such as the forearm flap can be used to reconstruct the nasal lining and combined with cartilage grafts to provide structural rigidity.35,36,37 A paramedian forehead flap is then used for external coverage. For such defects, postoperative radiation may be needed, and reconstruction should be delayed until adjuvant radiation has been completed. Alternatively, for extensive rhinectomy defects, the use of a prosthesis is also an option, and for many patients, a preferable one due to the excellent aesthetic and functional results and the convenience of not having to undergo multiple staged surgeries.38,39
Reconstruction of the Cheek and Face

For even larger defects of greater than one half the eyelid width, lid switch procedures are necessary to recruit the components of the posterior lamella in order to reconstruct the defect. The anterior lamellar defect is then reconstructed with a full-thickness skin graft from available upper eyelid skin. The most common lid switch procedure is the Hughes flap, which is a tarsoconjunctival flap that is passed from the donor lower eyelid to the defect resulting in a bridge of tissue, which obstructs the vision in that eye. A second procedure is necessary in order to divide the bridge of tissue. An analogous procedure for large defects of the upper lid is the Cutler–Beard flap, which involves harvesting a flap that includes the anterior lamella components as well as conjunctiva but lacks the structural support of the tarsal plate. The Cutler–Beard flap is a dermo-musculo-conjunctival flap and is supplemented with an auricular cartilage graft in order to replace the tarsus.

Note

Full-thickness defects that are less than a third of the eyelid are best closed primarily using a wedge-type closure paying careful attention to realign the lid margin.

25.9 Facial Nerve Reconstruction

All patients undergoing oncologic surgery that may include resection or division of the facial nerve should be examined preoperatively for facial nerve function and counseled accordingly about the potential need for reconstructive procedures. When the facial nerve is transected or resected, direct facial nerve repair or cable nerve grafting should be attempted in virtually all patients when the proximal and distal stumps of the facial nerve are available. Our own experience as well as that of others has confirmed that facial nerve recovery is possible, even in the setting of prior weakness, advanced age, or postoperative radiation therapy.44,45,46

When the proximal facial nerve is not available for repair/grafting, the distal nerve(s) can be grafted to redundant contralateral facial nerve branches or ipsilateral “donor” nerves, including the masseteric (V), hypoglossal (XII), or spinal accessory (IX). In recent years, the masseteric nerve has emerged as the preferred donor nerve for facial nerve transfer due to its effectiveness in producing strong contractions and minimal donor-site morbidity.47,48 This nerve exits the intracranial cavity via the foramen ovale and passes over the lateral pterygoid muscle and through the coronoid notch of the mandible to

Fig. 25.9 (a) Cheek and total nasal defect. (b) A cervicofacial advancement flap was elevated to cover exposed maxillary bone. (c) The nasal defect was left open. The patient will receive a nasal prosthesis once radiation is complete.
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enter the posterior surface of the masseter muscle near its origin beneath the zygomatic arch. It is found by careful lysis of the masseteric muscle fibers beginning at the posterior border of the mandible. The nerve usually takes an oblique course within the deep substance of the muscle, traveling from posterior superior to anterior inferior. Following the nerve distally allows adequate length to be gained for direct anastomosis to either the main facial nerve trunk when intact, or to the zygomatic and buccal branches, which are usually preferentially selected for reinnervation due to their important expressive and sphincter functions.

**Note**

The masseteric nerve is a preferred donor nerve for facial nerve transfer due to its effectiveness in producing strong contractions and minimal donor site morbidity.

When the distal branches of the facial nerve cannot be located or the facial muscles themselves are resected, facial symmetry can be restored by static reanimation procedures. Such procedures, including the brow lift, upper eyelid gold weight placement, lateral canthoplasty, and facial slings, should be considered for all patients with facial paralysis resulting from oncologic resection, even in some patients who have undergone nerve repair or grafting, depending on the degree of facial nerve functional impairment and expectations for recovery. Elderly patients with age-related brow ptosis, lower eyelid laxity, and skin redundancy, in particular, may benefit from static corrective procedures while awaiting partial or even total return of facial nerve function.

While periorbital static reanimation procedures can be performed at a later stage, to allow for a better assessment of the degree of facial motor dysfunction, it is often best to perform static cheek and mouth reanimation at the time of cheek reconstruction. This prevents needing to later dissect around flap pedicles as well as nerve repairs or grafts, if performed. If periorbital reanimation is not performed immediately at the time of cheek reconstruction, eye care should be emphasized to the patient postoperatively, including adequate lubrication and taping the eye shut while sleeping. Delayed gold weight placement allows for more accurate assessment of the exact weight needed to result in satisfactory eye closure without adding unnecessary weight which can make full eye opening difficult or cause the patient fatigue.

**Note**

Delayed gold weight placement allows for more accurate assessment of the exact weight needed to result in satisfactory eye closure without adding unnecessary weight which can make full eye opening difficult or cause the patient fatigue.

Free muscle transfer can be used to reanimate the lower face, mimicking the action of smiling while also providing tension on the corner of the mouth to prevent loss of oral competence and facial symmetry. Commonly used muscle free flaps for dynamic facial reanimation include the gracilis, latissimus dorsi, serratus anterior, and pectoralis minor muscles. Motor reinnervation of muscle free flaps can be achieved by utilizing a cross-facial nerve graft from a buccal branch of the contralateral facial nerve, usually in a two-stage procedure, or in a single stage to the masseteric nerve. One challenge of functional muscle transfer for dynamic lower facial reanimation in the setting of cheek malignancies is the substantial increase in operative time following resection and cheek reconstruction. Also, a question that remains unanswered is the reliability of reinnervation and muscular function when adjuvant radiation is administered. Because of these concerns, free muscle transfer is usually performed as an adjuvant procedure after all oncologic treatments have been completed and the patient is considered cancer-free.

### 25.10 Revisions and Refinements

The final objective in all reconstructive procedures is to restore form and function. Oftentimes the final result may be suboptimal either from an aesthetic perspective, functional perspective, or both. Further revisions in order to improve the contour, revise scars, or improve patients’ function may be necessary. Not infrequently, the impact of radiation is underestimated and can lead to dramatic changes in the appearance with contraction of the overlying skin as well as loss of volume. Fat grafting or “lipofilling” has been gaining in popularity and can be used to augment contour deficits that result following radiation. Alternatively, if the flap is excessively bulky, a simple operation to remove the volume via liposuction or direct excision can have a significant benefit to the overall appearance and final cosmetic result.

### 25.11 Conclusion

Cheek and facial defects can result from a variety of causes and reconstruction of such defects presents unique challenges to the reconstructive surgeon. Reconstruction should typically follow the reconstructive ladder with the aim of using local tissue when possible, paying careful attention to natural subunit boundaries and adjacent structures. However, for extensive defects, free tissue reconstruction is the standard of care and affords most patients an acceptable reconstruction that is able to restore both the functional and aesthetic concerns in facial reconstruction. The optimal reconstruction of extensive defects that cross facial subunits usually involves addressing each subunit separately. A discussion of facial nerve dysfunction and corrective procedures should be part of every consultation with patient who have potentially deep extension of facial malignancies.

### References


Reconstruction of the Cheek and Face


26 Carcinoma of Unknown Primary

Umamaheswar Duvvuri and Michael J. Persky

26.1 Introduction

Patients with head and neck squamous cell carcinoma (SCC) commonly present for evaluation of a neck mass. A neck mass in an adult is considered to be cancer until proven otherwise. Most commonly, carcinoma of the neck is secondary to a metastatic carcinoma from the upper aerodigestive tract. A patient with a biopsy-proven SCC cervical metastasis has a high likelihood of HPV-related disease. In a recent study evaluating patients diagnosed with CUP from 2005 to 2014 and found that 91% of these tumors were HPV-related. A thorough attempt at identifying the primary cancer is important as identification helps provide more accurate staging and prognostic information, as well as decreases the radiation field if the primary site is found. Ultimately, if a primary is not found, the treatment options include surgery, radiation, chemotherapy, or a combination of those three therapies. This chapter provides the background, workup, and treatment of patients with CUP, with a focus on advances in transoral laser and robotic surgery that have provided new techniques and options for both the diagnosis and treatment of CUP.

It should be noted that patients with a supraclavicular mass are more likely to have a primary source from either the skin or an infraclavicular area (such as breast, esophagus, lung, or ovary). The workup of these supraclavicular masses is not discussed here.

26.2 Epidemiology/Etiology of the Disease

CUP currently accounts for 3% of all head and neck malignancies, though the incidence appears to be increasing. Classically, these patients are men between 55 and 65 years. They are often heavy smokers with varying alcohol intake, and they most often present with complaints of a neck mass. Recently, this demographic has shifted, however, with younger patients presenting who suffer from human papillomavirus (HPV)-related oropharyngeal cancer. New studies demonstrate that patients with CUP will more likely have an HPV-related tumor status than an HPV-negative tumor status. Compared to the classically non-HPV-related patients described above, patients with tumors who are HPV-related CUP are approximately 10 years younger, male, and nonsmokers. A single-institutional retrospective study evaluated patients diagnosed with CUP from 2005 to 2014 and found that 91% of these tumors were HPV-related.

The majority of patients with HPV-associated carcinoma present with a neck mass. Many of these patients harbor a small primary carcinoma, hidden in the base of tongue (BOT), which is difficult to identify on a physical examination, or even with imaging. The rise in CUP incidence is likely a direct result of the HPV epidemic. In the majority of patients who present with CUP, the primary tumor is HPV positive and will be found within the cryptic lymphoid tissue of the lingual or palatine tonsils. Of course, it is important to consider all upper aerodigestive sites as well as skin when looking for the primary. Ultimately, if the primary is never found, it is for one of two reasons: it is too small and missed by imaging and/or a pathologist, or the primary tumor was destroyed with an immune-mediated response that the metastatic tumor escaped.

Note

In HPV-associated CUP, if the primary carcinoma is not found, it may be that the primary cancer was so small that it was missed by the pathologist, or the carcinoma was eradicated by the patient’s immune-mediated response.

26.3 Staging

The eighth edition of the American Joint Committee on Cancer (AJCC), which started in 2018, describes the TNM staging paradigm for CUP. This new edition stages CUP positive for HPV (or p16, a useful surrogate biomarker for HPV infection) or Epstein-Barr virus (EBV) differently from CUP negative for HPV and EBV. According to the new system, HPV-associated CUP is considered oropharyngeal origin, and so if the specific primary site cannot be found after physical exam, imaging and surgical endoscopy, the patient is categorized with T0 HPV-associated oropharyngeal carcinoma. The same is true of EBV-associated CUP, except in this case the origin is assumed to be the nasopharynx and the patient is designated with T0 EBV-associated nasopharyngeal carcinoma. The Tx stage applies to HPV and EBV negative CUP, because a primary site cannot be assumed and so one is not assigned.

The N-staging of head and neck squamous cell carcinoma also depends on HPV or EBV-positivity, but is not addressed here.

26.4 Prognostic Factors

All appropriate attempts should be made to find the primary cancer, as identification of a primary portends a better prognosis regarding overall, cause-specific, and disease-free survival. If the neck node is HPV-positive, the chance of finding the primary is increased. HPV-related CUP has been shown to have a significantly better 5-year overall survival than HPV-negative CUP (80 vs. 37%). This likely reflects a less aggressive biology of the disease accompanied with an improved response to treatment. Epidermal growth factor receptor (EGFR) expression can also serve as a negative prognostic marker. HPV-related tumors are less likely to express EGFR, and patients with HPV-positive/EGFR-negative tumors have been shown to have the best 5-year disease-free survival (93%). However, a tumor that is EGFR-
positive can be directed toward targeted immunotherapy to block these receptors.

**Note**
EGFR expression can be used to prognosticate and direct therapy in the CUP patient.

### 26.5 Clinical Presentation

Patients with CUP will commonly present with a neck mass. This mass is commonly found in level II, implicating the oropharynx as the likely site of primary.\(^5\,\text{,}\,\text{1}\) A level III mass suggests the primary is within the hypopharynx or supraglottis, while a level IV or supraclavicular mass points to an infraclavicular primary.\(^1\)

It is important to take a thorough history with an emphasis on tobacco and alcohol intake. Given the role of HPV in oropharyngeal cancer as well as CUP, patients should be asked about sexual and oral sexual activity, as increasing partners make it more likely to have a head and neck HPV infection.

Complaints of voice changes, swallowing difficulty, odynophagia, otalgia, or difficulty breathing can help point to the site of primary cancer. Finally, patients should be questioned about their dermatological history.

**Note**
In addition to questions related to odynophagia, dysphagia, and dysphonia, CUP patients should be asked about their dermatological history as primary skin cancers are a common cause of CUP.

### 26.6 Diagnosis and Workup

The goal of evaluation is to establish a histological diagnosis as well as identify the site of the primary disease.

Any patient with a neck mass suspicious for cancer should undergo a thorough head and neck evaluation. The mass should be palpated to determine if the node is fixed to other structures in the neck or if it is mobile. The rest of the bilateral cervical nodal basins should be examined, as well as the thyroid and salivary glands. The oral cavity and oropharynx should be bimanually palpated with special attention to the tonsillar fossae and the BOT. Note that there is a 10% incidence of contralateral metastasis from tonsillar SCC, so be sure to evaluate all sites bilaterally.\(^1\)

Utilize flexible fiberoptic nasopharyngolaryngoscopy to evaluate the nasopharynx (with particular attention to the fossa of Rosenmüller), tonsils, BOT, supraglottis, and hypopharynx.

**Note**
There is a 10% incidence of contralateral metastasis from tonsillar SCC, so be sure to evaluate all sites bilaterally.
Fig. 26.2 The supraglottic larynx is drained through levels II and III.

Fig. 26.3 The primary drainage pattern of the lateral oral tongue. Lymphatic drainage is primarily into levels II and III.

Fig. 26.4 Lymphatic drainage of the nose and nasopharynx. The primary direction of drainage from the nasopharynx is laterally into the lateral retropharyngeal lymph nodes and levels II and V.

Fig. 26.5 Lymphatic drainage for the soft palate and the base of the tongue. The soft palate drains both anterior into levels IA and IB and posterior into levels IIA and IIB, and the base of the tongue drains into levels IA and IIB.
Lymphatic drainage of the hypopharynx is to levels II, III, and IV (Fig. 26.7).

Attempts should be made to obtain a tissue diagnosis of the neck mass. A fine-needle aspiration biopsy (FNAB) is an efficient means to obtain a cellular sample. Usually, a palpable mass can be accessed without the help of ultrasound, but many HPV nodal metastases are cystic and ultrasound (US) can help direct the needle to the wall of the cyst to improve diagnostic success.\(^{13}\)

The cytology sample should be evaluated for HPV as well as EBV—this can help locate the primary as well as provide prognostic information. As noted above, histological detection of HPV suggests that the primary is located in the oropharynx and portends a good prognosis. Immunohistochemical analysis of p16 also serves as a useful biomarker of HPV infection. EBV infection is a sensitive marker for nasopharyngeal carcinoma. It should be stated that if the cells are HPV and EBV negative, an oropharyngeal or nasopharyngeal primary cancer should not be ruled out.

**Note**

If the neck mass cytology is HPV and EBV negative, an oropharyngeal or nasopharyngeal primary cancer should not be ruled out. A patient may still harbor an oropharyngeal or nasopharyngeal primary cancer when HPV/p16 and EBV are negative, respectively.

If the sample is nondiagnostic, it should be attempted again. Do not do an open surgical biopsy or excision until imaging has been performed as this may result in false-positive radiologic results due to inflammation and tissue changes.

The first-line imaging modality for patients with CUP is computed tomography (CT) with contrast or magnetic resonance imaging (MRI) with contrast of the neck. If the primary site is not identified, a positron emission tomography with CT (PET/CT) can be helpful. In a prospective study, a preendoscopy PET/CT was shown to detect the primary 37% of the time. In patients who already underwent an unsuccessful diagnostic endoscopy, the rate of identification via PET/CT is lower, at 27%.\(^{14}\)

When a patient has FNA-proven SCC in a cervical lymph node, but a physical examination and imaging do not reveal the primary site, the patient should undergo panendoscopy with directed biopsies of the bilateral base of tongue (BOT), nasopharynx, and pyriform sinuses. A bilateral tonsillectomy should be performed, as there is a noted 10% incidence of contralateral metastasis from tonsillar SCC.\(^{12}\)

If the FNA is p16 or HPV positive, the surgeon should have a high index of suspicion for a primary within the crypts of the oropharyngeal lymphoid tissue. In this circumstance, the patient may benefit from a robotic or transoral laser BOT resection at the time of endoscopy. The goal is to remove the entire lingual tonsil under high magnification in order to identify the primary site.
26.7 Transoral Robotic Surgery Technique

The patient should be supine, orally intubated with a small 6–0 endotracheal tube taped to the side opposite the entry of the robot. The table should be turned 180 degrees. The maxillary teeth should be protected. The Dingman or Crowe–Davis retractor may come with a soft tooth guard—if not, molded aquaplast works well, and is smaller than a standard tooth guard. We find that the tongue may be lacerated by the mandibular incisors, so fashion aquaplast to cover them as well.

Use a Dingman or Crowe–Davis retractor to gain exposure. It is important to take the time to get an appropriate view with a headlight—the circumvallate papillae and lateral pharyngeal walls should be seen, as well as a glimpse of the epiglottis. After suspension of the retractor, bring the robot into position. Set up a Maryland grasper and a cautery Bovie to perform the dissection.

The first incision should be along the circumvallate papillae from the left to the right side. Then bisect the lingual tonsil with a superior to inferior incision to the vallecula. Each side will be dissected out separately. The plane of dissection is just superficial to the BOT musculature. Some advocate removing a sliver of muscle with the goal of obtaining a negative margin if the primary tumor is found. Avoid penetrating deep into the muscle in order to protect the lingual artery and subsequent blood loss. The dissection should be from the midline to lateral, starting superiorly. Take care to transect the glossotonsillar fold and remove tissue from the glossotonsillar sulcus—any tissue left behind may harbor the subcentimeter primary (Fig. 26.8). Carry the dissection inferiorly to the vallecula—identify the vallecula by its minor salivary glands. Control any small blood vessels with electrocautery. Take caution to avoid damaging the epiglottis, as well as other supraglottic structures. Once the side ipsilateral to the cervical metastasis is complete, proceed to the contralateral side.

Be sure to orient the specimen for the pathologist.

26.8 Complications of TORS

A recent retrospective, multi-institutional cohort study of 305 patients found that the overall complication rate for patients undergoing TORS to resect oropharyngeal cancer is 7.9%. The same study found that pneumonia was the most common complication and revealed an overall mortality rate of 0.7%. The complication with the greatest risk of morbidity is injury to the lingual artery. This has the potential to hemorrhage postoperatively, which can be life threatening. The postoperative hemorrhage rate is 5 to 8%. Given that the robotic lingual tonsillectomy does not resect significant tongue musculature, the artery can be avoided. As with a simple tonsillectomy, however, the eschar covering the surgical defect can slough off days to a week after the operation, which can cause new-onset bleeding. This can usually be managed with observation or topical cautery. If the bleeding is significant or posterior, the patient may need to go to the operating room for control.

26.9 Postoperative Care

It is appropriate to extubate the patient in the operating room and have the patient monitored overnight. The patient will have significant pain, which should be managed with intravenous narcotics. High-dose proton pump inhibitors and H2 blockers, along with standard reflux precautions, decrease irritation of the wound. In the same vein, sucralfate will help minimize reflux.

Patients are usually ready for a soft diet on postoperative day 1. Having a patient work with a speech pathologist is useful to manage dysphagia. Avoidance of clear liquids in the immediate postoperative period is important as it is the most difficult consistency to swallow without aspirating. Once pain is
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controlled, the patient may advance the diet as tolerated. The patient is usually home by postoperative day 1.

26.10 Role of Neck Dissection in CUP

For patients with low-volume HPV-related neck disease, primary neck dissection is an option for definitive treatment. In other words, a patient with low volume neck disease, without likely extracapsular spread on imaging or examination, may be treated with ipsilateral selective neck dissection of levels II through IV. This can be performed at the time of the endoscopic / robotic search for the primary or 1 to 2 weeks later.

Note
For patients with low-volume HPV-related neck disease, primary neck dissection is an option for definitive treatment.

A benefit of performing the neck dissection at the same time as TORS is the ability to tie off branches of the ipsilateral external carotid to help avoid postoperative hemorrhage. Ideally, the lingual, ascending pharyngeal, and facial arteries should be tied. A benefit of staging the neck dissection until after TORS is that the final pathology report may show a close or positive margin that could undergo re-resection while in the operating room for the neck.

If the primary site is identified, and the pathologic stage of the neck remains low volume with no extracapsular spread (ECS), it is appropriate to closely observe the patient without subjecting them to adjuvant treatment. For a high N-stage, the current practice is to treat the patient with adjuvant radiation versus concurrent chemoradiation, depending of the patient’s risk.

26.11 Radiation in CUP

Per current National Comprehensive Cancer Network (NCCN) guidelines, radiation can be used as primary or adjuvant treatment for CUP. Unimodality treatment with radiation is recommended for N1 disease. More recently, some will treat N2a disease with radiation alone given then excellent clinical response to HPV-related CUP. In higher-staged disease, adjuvant radiation is used after neck dissection, as discussed above, or concurrently with chemotherapy if surgery is not appropriate.

The current standard radiation technique for CUP is salivary-preservation intensity-modulated radiation therapy (IMRT). Bilateral mucosal sites and bilateral necks are irradiated. The retropharyngeal nodes are also routinely irradiated. When this is done, locoregional recurrence is rare—the most common recurrence is distant metastatic disease.

Note
The current standard radiation technique for CUP is salivary-preservation IMRT with radiation of the retropharyngeal nodes.

The dose of radiation to the neck in patients with unknown primary is taken from experiences with known primary. Areas with gross disease receive 66 to 70 Gy; high-risk areas for adjuvant radiation receive 60 to 66 Gy; low-risk areas where there is concern for microscopic disease receive 45 to 54 Gy. Mucosal sites receive 50 to 64 Gy, depending on the institution. Those who use lower doses cite subclinical disease burden that requires less irradiation. The institutions using higher doses contend that the primary is likely in the oropharynx and these areas should be treated similarly to primary disease.

26.12 Chemotherapy in CUP

Chemotherapy is used concurrently with radiation as definitive treatment for patients with N2a and higher disease. The main benefit of systemic therapy is locoregional control.

Chemotherapy is used in the adjuvant setting for patients with ECS. However, it should be noted that recent studies show that most ECS in these patients will be less than 1 mm and will respond similarly to treatment as disease without ECS. Given the potential toxicity of chemotherapy, clinical trials are underway to deintensify treatment so that minimal ECS is not treated with this systemic therapy.

Current well-designed clinical trials are underway that investigate de-escalation of these HPV-positive CUP—to decrease the need and dose of radiation in low-risk patients, as well as to avoid the use of chemotherapy.

26.13 Posttreatment Surveillance

Approximately 12 weeks after the completion of definitive treatment, the patient should undergo a PET/CT to evaluate response. A patient treated with surgery alone should have no evidence of residual disease. A patient treated with radiation or chemoradiation should have a complete response.

26.14 Clinical Case

A 44-year-old woman with a neck mass and a nondiagnostic FNAB from an outside physician.

26.14.1 Presentation

A 44-year-old woman with no smoking or drug history presented with a right neck mass. She stated that she noticed it while applying moisturizer 2 months ago. Her primary care physician treated it with two courses of antibiotics, but it did not decrease in size. She had no symptoms from it. She was referred to a head and neck surgeon after her primary care physician obtained a CT scan with contrast of the neck, which revealed a 2.5-cm cystic mass in her right neck in level II without signs of ECS.

26.14.2 Diagnosis and Workup

Examination in the office only revealed a solitary palpable, mobile mass. There was no mass seen or palpated within the upper aerodigestive tract, including all parts of the pharynx
and larynx. An office FNA was performed with a pathologist who determined the sample was adequate. It returned as HPV + SCC. She was sent for a PET/CT in an attempt to find a primary lesion in her upper aerodigestive tract, but there was only uptake in the known mass. At this point, the patient was staged T1N1MO.

26.14.3 Treatment Options

This patient was presumed to have metastasis from the lymphoid tissue in Waldeyer’s ring. She is a nonsmoker, with minimal neck disease, putting her at low risk of death from disease. The patient needed to undergo appropriate attempts to find the primary tumor, and the most complete method of doing so is performing direct laryngoscopy and then resecting all the lymphoid tissue of Waldeyer’s ring. The benefit of removing all lymphoid tissue is the potential of resecting the tumor with negative margins in the process. Another option is bilateral tonsillectomy and directed biopsies of the BOT—the primary may be extirpated if in the tonsil but will only be sampled if in the BOT (the more likely source).

The potential treatments after endoscopy with lingual tonsillectomy were discussed. Given her minimal neck disease burden, she could receive primary radiation to the ipsilateral neck and primary site. However, if the primary tumor was completely excised (or not identified after the complete removal of Waldeyer’s ring tissue, making her T0), she could avoid radiation to the aerodigestive tract all together. Moreover, if she underwent a neck dissection and her N stage remained N1 with no ECS, she could avoid adjuvant radiation to the neck as well. Given her age, she wanted to avoid the long-term effects of radiation and opted for a robotic resection of the bilateral lingual tonsils with a right selective level II through IV neck dissection. The tumor was found in the right tonsil, 3 mm, and excised with negative margins. The neck dissection revealed one positive lymph node, 2.3 cm without ECS, and 26 benign lymph nodes. She is being closely observed without adjuvant treatment.

References


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Peter M. Som and Eric M. Genden

27.1 Introduction

It has been estimated that each year, more than 400,000 new cases of head and neck cancer will be diagnosed and that these represent 5.4% of all cancers with an average overall risk of death of 40%.\(^1,2\) Regardless of the treatment protocol for patients with a primary head and neck cancer, it has been demonstrated that when cancers are diagnosed early, the rate of survival and cure rates are improved.\(^3,4,5,6\) Similarly, it has been suggested that the earlier recurrent disease is identified and treated, the better the quality of life, the longer the survival, and possibly the better the chance for cure, although this remains somewhat speculative. In addition, the cost of patient care is less, the earlier a recurrence is diagnosed.\(^7\)

In spite of the fact that the majority of treatment initiatives have been directed toward providing a cure, over the past several decades there has been little improvement in the cure rate for most patients with head and neck cancer.\(^8,9,10,11,12,13,14,15\) Although the percentage of patients cured may have changed little, their disease-free survival appears to be improving, and most patients are now dying from distant metastases or from second primary tumors rather than from local or regional recurrences.\(^9,10,11\) Therefore, although the cure rate of patients with a recurrence of a head and neck cancer may be little affected by contemporary combined modality therapy, as noted, the opportunity to provide prolonged disease-free survival with an acceptable quality of life is the goal and commitment of a surveillance program.\(^9\)

Note

The goal of a surveillance program is to provide prolonged disease-free survival with an acceptable quality of life.

27.2 Considerations for a Surveillance Program

Routine clinical examinations form the basis of any surveillance program, and it is a common practice for clinicians to see patients every 2 to 3 months for the first 24 months after initial therapy. If one were to wait for a recurrence to cause a noticeable mass or pain, it is likely the recurrence is already large. Imaging with computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography fused with either CT or MRI (PET/CT and PET/MRI) now offers the opportunity to identify early recurrences before they become clinically evident. Thus, imaging studies should be coordinated with periodic clinical visits to identify recurrent disease, the presence of a second primary tumor, or a metastasis prior to clinical presentation.\(^5,12,13,15\) The addition of such imaging to the clinical evaluation is especially germane to the posttreatment neck, which is often stiff and “woody,” making it difficult to palpate a deeply situated mass. Many of these posttreatment necks are also insensate, making the presence of a recurrence mass more difficult to clinically diagnose. A surveillance program should also take into consideration high-risk patients with a history of advanced disease, low neck metastasis, extracapsular nodal spread, continued smoking and/or alcohol abuse, and the adverse histological prognosticators such as perineural invasion and limited lymphocytic response.\(^16,17,18,19,20\) These patients will require more vigilant follow-up and more aggressive treatment.

There are sufficient data to support the notion that the majority of recurrences and deaths resulting from head and neck cancers occur within the first 1 to 2 years after initial treatment.\(^5,21\) This implies that any surveillance program should be most diligent during this time period. The recurrence rate decreases slightly during the next 2 years and, after that, the recurrence rate notably diminishes. Thus, a surveillance program should consist of periodic coordinated clinical and imaging studies every 3 to 4 months for the first 2 posttreatment years, then every 6 months for the next 2 years, and finally yearly. The long-term surveillance recognizes that once a patient has one upper aerodigestive tract cancer, there exists the threat of a second primary tumor, be it synchronous or metachronous. The incidence of such a second primary tumor varies from 5 to 36%.\(^2\) As these second primary tumors or metastases may take years to develop, long-term (annual) surveillance should be a part of the program.

Note

There are sufficient data to support the notion that the majority of recurrences and deaths resulting from head and neck cancers occur within the first 1 to 2 years after initial treatment.

The PET/CT or PET/MRI studies should consist of an initial whole-body study followed by a dedicated head and neck study (thinner slices, smaller field of view yielding better resolution). The whole-body study allows detection of distant metastases as well as a distant second primary tumor.

Because pulmonary metastasis is the most common site for distant metastasis, pulmonary surveillance should be a part of any head and neck cancer surveillance protocol. This can be best accomplished by periodic CT scans and/or coregistered PET/CT scans. In addition, if PET/CT is utilized as a pretreatment (staging) study, it also offers the possibility of identifying not only a clinically silent metastasis, but also a second primary tumor (in the chest, abdomen, or pelvis) prior to initial therapy for the head and neck cancer.\(^1,2,22,23\)

Note

Pulmonary surveillance should be a part of any head and neck cancer surveillance protocol.
27.2.1 Morphologic Imaging

There are two distinct choices for a morphologically based imaging modality to utilize in a surveillance protocol: CT and MRI. Each has its unique benefits. CT has been shown to be more accurate than MRI in identifying pathologic cervical adenopathy.24 Typically, a current CT examination of the neck takes approximately 10 seconds after contrast administration. For patients in pain and/or having difficulty with their secretions, this short scan time is a great benefit. By comparison, typical MRI scanner times for each sequence are between 4 and 7 minutes, with the entire study taking approximately 45 minutes. Compared with CT, MRI may be more sensitive to artifacts from body movement, vascular pulsations, rapid respirations, and repeated swallows, all of which may be present in patients with head and neck cancer. As noted, many of these patients have difficulty lying supine for a prolonged time because of dyspnea, pain, or difficulty handling their secretions. This discomfort is often manifested as restlessness and/or rapid breathing while lying supine, causing motion artifact on the MRI study. Thus, because of considerably shorter scan time, CT is the preferred modality for these posttreatment patients.

In contrast, if there are numerous surgical clips in the neck that cause significant degradation artifacts on CT, such artifacts tend to be greatly reduced on MRI. Contrast MRI is superior to CT in identifying tumor extension through the skull base and dura, and the closer to the skull base, the more may be the advantage of MRI over CT scanning. Lastly, dental amalgams may cause severe degradation artifacts on CT images through the oral cavity. Such artifacts tend to be less degrading on MRI scans, and MRI may be better for assessing disease in this region.25 On the average, approximately 10% of patients reject the MRI study due to claustrophobia, and patients with most pacemakers cannot have the study. Patients with metallic body fragments or some implants also may not be able to have the MRI examination.

The main rejection-related problem with contrast CT studies is patient allergy to iodine-based contrast agents, a problem that in most cases can be overcome by premedicating these patients with steroids. A consideration of study costs reveals that, in general, a contrast CT study is about one-third the cost of a contrast MRI study. Finally, access to CT scanners is, in general, easier than it is to MRI scanners. Taking all of these factors into account, we considered CT to be the preferential morphologic imaging study. This is also especially germane if PET/CT examinations are incorporated into the surveillance plan, as the CT portion of the study can be compared with prior CT studies (apples to apples, not apples and oranges). As discussed, however, in selected cases, an MRI study may be more appropriate and become the modality of choice for those patients. This is more easily obtained as at present PET/MRI is becoming more available.

27.2.2 Positron Emission Tomography

[18F] Fluoro-2-deoxy-D-glucose (FDG)-PET scanning is issuing in a new era of molecular imaging. There is, however, confusing literature on how and when best to utilize this modality. There is little controversy regarding a negative PET study as the negative predictive value (NPV) of PET is between 90 and 95%. This high figure has suggested to many physicians that the best way to utilize PET is for its NPV.26,27 The current resolution of PET scanners is of the order 3 mm, and although a negative PET does not completely rule out the presence of tumor, it does strongly suggest that no gross tumor mass is present and that no further immediate treatment may be indicated.

However, when a PET scan shows an area of increased avidity in the neck, the exact cause of this increased standard uptake value (SUV) is less clear. The differential diagnosis includes tumor, inflammation, and granulation tissue in response to treatment, as well as more established causes such as infection, increased muscle activity and/or hypertrophy, the presence of surgical hardware, normal accumulations within the major salivary glands and/or soft palate, brown fat, and benign tumors.

Thus, there is a real possibility of a false-positive PET study, especially in the 3 months immediately following the end of the initial treatment. PET studies alone have been reported to have a positive predictive value between 65 and 80%.28,29 However, if the area of increased avidity is further localized with contrast CT and/or MRI, many of these false-positive areas can be eliminated as sites of tumor recurrence. For PET/CT studies performed after radiation for head and neck cancers, the sensitivity improved from 55 to 95% and the NPV increased from 90 to 99% when comparing studies done 1 month after treatment with studies performed more than 1 month after treatment.29,30 In addition, PET studies performed within the immediate post-treatment period may be falsely negative. This is the result of decreased fluorodeoxylucose (FDG) reaching the tumor due to altered tumor vascularity and decreased FDG uptake as a result of radiation and chemotherapy.

Today, it is generally accepted, that in order to obtain a reliable PET/CT or PET/MRI study, it is best to wait a minimum of 3 months after treatment. Thus, PET/CT and PET/MRI have become the primary imaging modalities in the initial evaluation of a head and neck cancer patient as well as in the surveillance of these patients.31,32 In addition, recent studies have shown that the SUV value of the primary tumor on an initial pretreatment PET/CT study may directly correlate with outcome. However, this relationship was not shown to be reliable for nodal
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had a negative PET/CT study 3 months after radiation therapy, (NED) for residual metastatic adenopathy in the neck, and who deems further studies unnecessary.

ment algorithms. It is generally accepted that in order to obtain a reliable PET/CT or PET/MRI study, it is best to wait a minimum of 3 months after treatment.

Note

It is generally accepted that in order to obtain a reliable PET/CT or PET/MRI study, it is best to wait a minimum of 3 months after treatment.

27.3 The Mount Sinai Surveillance Protocol

27.3.1 Pretreatment and Surveillance Protocol

All patients receiving treatment for a head and neck cancer undergo a pretreatment PET/CT, which includes coverage of the neck, chest, abdomen, and pelvis. All of the CT studies in the protocol should be performed as contrast-enhanced examinations unless contrast cannot be administered because of a severe allergy or a contraindicated medical condition. The field of view (FOV) for the neck CT is approximately 25 cm, with a reconstructed scan thickness of 1 to 3 mm. To avoid beam hardening artifact, the patient's arms are lowered to their sides for the head and neck portion of the study. When the chest/abdo- men/pelvis portion of the CT examination is performed, the FOV is between 36 and 40 cm and the patient’s arms are raised over their head. The FOV for the PET portion of the studies should correspond with the CT FOV values mentioned above. A similar protocol should be utilized when a PET/MRI study is performed.

27.3.2 Posttreatment Assessment

A baseline CT scan is obtained 4 to 6 weeks after initial treatment has been completed. This creates a posttreatment CT study to which future examinations can be compared. Taking into account the notion that the greatest surveillance should be in the first 2 posttreatment years, we recommend that patients have PET/CT studies every 3 to 4 months for the first 2 post- treatment years. We start the cycle with a PET/CT scan 4 months after treatment. The surveillance continues with PET/CT studies every 6 months for the third and fourth posttreatment years. Finally, patients should have yearly PET/CT studies ongoing from the fifth posttreatment year or until the physician deems further studies unnecessary.

The use of PET/CT and PET/MRI is clearly influencing treatment algorithms.

In a recent study of patients who had no evidence of disease (NED) for residual metastatic adenopathy in the neck, and who had a negative PET/CT study 3 months after radiation therapy, none of them developed regional disease, and surgery could be withheld. Even if small residual was seen on CT or MRI, but it was PET/CT negative, surgery could be withheld. Although this concept is not yet held by all physicians, the PET/CT results are definitely influencing treatment algorithms.

The management of the treated head and neck cancer patient has always been a challenge; however, we believe that the combination of coordinated physical examination and PET/CT and/or PET/MRI has the potential to provide accurate information regarding the preclinical presence of both recurrent tumor and second primary tumors. It is hoped that this information will lead to better treatment decisions and better patient outcomes. The use of PET/MRI may be especially useful in patients with postsurgical hardware. The future of PET/CT lies with new agents that will better differentiate between tumor and inflammatory reaction. Many such agents are currently on the horizon, and it is hoped that soon they will be clinically available to help more quickly and definitively identify recurrent disease.

Note

The use of PET/MRI may be especially useful in patients with postsurgical hardware.

27.4 Clinical Cases

The following example cases serve to demonstrate the decision problems encountered by clinicians when they are faced with a positive surveillance PET/CT study.

27.4.1 Case 1

A 56-year-old man had a T1 anterior tongue carcinoma surgically removed. He was treated with radiation therapy after surgery and comes for a PET/CT study 4 months after treatment. Clinically, he is NED. His PET/CT study shows diffuse activity within the tongue and two foci of activity in the posterior larynx (Fig. 27.1). What is the most likely cause of these findings, and what is the next clinical step in following this patient?

Discussion

The PET examination takes from 1 to 2 hours to perform, and during the examination, most patients talk to the physicians and technicians. The PET/CT is simply showing normal activity within the tongue muscles and within the cricoarytenoid muscles of the larynx (Fig. 27.2). There is no evidence of a focal tumor mass. With an essentially negative PET/CT study, this patient can be watched until the next planned observation point.

27.4.2 Case 2

A 62-year-old woman had a history of oral cavity cancer treated surgically 2 months ago. She then had a left second molar mandibular tooth extracted, and the extraction site did not heal. Shortly after that, she developed left level I adenopathy. Her PET/CT study shows focal uptake in the molar tooth area (Fig. 27.3) and mild activity in the level I nodes (Fig. 27.4).
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**Fig. 27.1** PET/CT study from case 1 showing diffuse activity within the tongue and two foci of activity in the posterior larynx.

**Fig. 27.2** PET/CT study from Case 1 showing normal activity within the tongue muscles and within the cricoarytenoid muscles of the larynx. No evidence of a focal tumor mass is present.
Surveillance of the Patient

Fig. 27.3 PET/CT study from Case 2: focal uptake in the molar tooth area.

Fig. 27.4 PET/CT study from Case 2: mild activity in the level I nodes.
Sclerosis rather than bone destruction was seen in the mandible on the CT scan. What is the most likely cause of these findings, and what is the next clinical step in following this patient?

**Discussion**

The absence of bone destruction and the presence of sclerosis on the CT scan makes carcinoma invasion of the mandible unlikely and chronic inflammation likely. The level I nodes could be either reactive or metastatic, as they only have a low SUV (2.7). Both the tooth extraction site and a level I node were biopsied, without evidence of tumor. This case demonstrates how inflammatory disease can mimic tumor recurrence. The patient was watched carefully over the next 2 to 3 months with no evidence of tumor recurrence. She has remained disease-free for 1 year after this study.

**27.4.3 Case 3**

A 68-year-old man had a right stage II tongue cancer and a IIB right neck node. He underwent extirpation of the primary tumor with a flap reconstruction and a right neck dissection. He comes for his 4-month posttreatment PET/CT study, and a focus of increased activity is identified around one of the clusters of surgical clips (▶ Fig. 27.5). What is the most likely cause of this finding, and what is the next clinical step in following this patient?

**Discussion**

Nontumorous increased PET activity can occur around surgical clips presumably due to local low-grade inflammation; however, in this clinical setting, a small tumor mass cannot be excluded, especially as the artifact from the clips on the CT scan obscures visualization of any small soft tissue mass. The site of increased PET activity should be biopsied using either an ultrasound-guided or CT-guided technique to ensure that the correct area was biopsied. At least five needle passes should be made to maximize the chances of getting tumor in the specimen. A cytologist, if possible, should be present to ensure sample quality. Such a CT-guided biopsy was performed, and no tumor was found. This patient was watched carefully over the next 18 months, and his PET/CT studies have remained unchanged. He is clinically disease free.

**27.4.4 Case 4**

An 84-year-old woman presents with a left tongue mass and a fixed left tongue. Her initial PET/CT study (▶ Fig. 27.6) shows increased activity in the tumor bed. Her tongue carcinoma is treated with brachytherapy. She has been well for 10 months and now returns with pain in the treated area. Her follow-up PET/CT study (▶ Fig. 27.7) shows some activity within the tumor bed. What is the most likely cause of this finding, and what is the next clinical step in following this patient?

**Discussion**

This PET/CT study was performed 10 months after the completion of her brachytherapy treatment. It was performed off protocol schedule because the patient developed pain. The increased activity within the primary tumor site indicates the presence of tumor, as any reactive change from the radiation therapy should have resolved by this time. A biopsy confirmed the presence of tumor. Because of her age and associated health issues, only palliative care was given.

**27.4.5 Case 5**

A 47-year-old man had a left tonsillar carcinoma with an N0 neck. He was treated with a chemoradiation therapy regimen. He comes for his 4-month PET/CT scan, which shows activity in left level II nodes (▶ Fig. 27.8). What is the most likely cause of this finding, and what is the next clinical step in following this patient?

**Discussion**

By 4 months after radiation therapy, any associated reactive changes should have resolved. Thus, the notably increased activity with the left level II nodes strongly suggests the presence of tumor. This patient had a neck dissection, and these were the only positive nodes in the specimen.

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**Fig. 27.5** Four-month posttreatment PET/CT study from Case 3 displaying a focus of increased activity around one of the clusters of surgical clips.
**Surveillance of the Patient**

**Fig. 27.6** The initial PET/CT study from Case 4 shows increased activity in the tumor bed of an 84-year-old woman.

**Fig. 27.7** Follow-up PET/CT study demonstrating very mild activity within the tumor bed.
Fig. 27.8 The 4-month PET/CT scan of a 47-year-old man (Case 4) who had a left tonsillar carcinoma with an N0 neck and was treated with a chemoradiation therapy regimen. The scan shows activity in left level II nodes.

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References


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drug development and emerging therapies that are likely to enter clinical practice in the near future. While a comprehensive review of all head and neck tumor biology, immunology, and targeted therapeutics would encompass a textbook by itself, this chapter will focus on the drug development process, using cetuximab, the only currently approved targeted therapy for HNSCC, as a case example. Additionally, novel clinical trial designs and the role of immunomodulatory therapy will also be discussed.

28.2 Drug Development: The Cetuximab Story

The development of a new drug intended for human use begins with in vitro studies. This initial preclinical phase may last for 4 to 5 years until a drug is deemed ready to begin a clinical trial. The goals of early benchwork experiments are to determine preliminary toxicity, efficacy, and pharmacokinetics. Results from in vitro and in vivo animal studies help researchers identify which novel compounds merit further investigation in the form of a clinical trial.1

The clinical assessment of a new therapeutic compound consists of four distinct phases, and each is intended to answer a specific question. A phase I study is intended to determine drug dosage while a phase II study determines its efficacy. In a phase III clinical trial, the drug is compared to other commonly used treatments, and finally a phase IV study investigates long-term side effects after regulatory approval. The complete process moving through each phase typically takes 10 years (> Fig. 28.1). The estimated development cost of a drug reaching U.S. Food and Drug Administration (FDA) approval is as high as $1 billion. The attrition rate of anticancer drug candidates from phase I studies to drug registration is striking: Over 95% of drugs tested in phase I studies do not reach registration.2 In this section, we further describe each phase of a clinical trial and use the development of cetuximab as an example.

28.2.1 Preclinical Phase

New drugs are discovered by several different mechanisms. At the molecular level, as a particular disease process is studied, a drug may be developed which either enhances or blocks a key regulatory step. Loss of cell signaling capabilities may negatively affect diseased cells resulting in an overall halt of disease progression. Drugs already used for a particular disease may be found to be beneficial in other disease types. In the era of genomic mapping, we now have a greater understanding of the role of certain genetic mutations associated with different types of cancer. Thus, with a comprehensive understanding of tumor biopsy and signaling, protein structural biology, and biochemistry, novel drugs may be specifically developed to inhibit or activate key proteins within oncologic signaling pathways. Whatever the method of initial drug discovery, once a particular compound is identified, it is further studied in a sequence of in vitro studies followed by in vivo animal studies. The role of these studies is to identify the best drug with the highest likelihood of efficacy and gather more information about dosing and toxicity in anticipation of a clinical trial. However, preclinical studies tend to be very costly and inefficient with relatively few compounds proceeding to a phase I clinical trial. Possible areas of improvement include both a better understanding of the targets that are of relevance to each tumor type, as well as better preclinical models representing more of human tumor biology.

While preclinical studies in cell lines and xenografts are a useful tool to screen compounds and might provide useful early signs of interest, they have not shown good correlation with efficacy in phase II trials or survival advantage in phase III trials. Better preclinical models to assess toxicity or test different formulations are also needed. Too many drugs that go into phase I/II clinical trials still have excessive toxicity or formulation problems that preclude further clinical development of potent inhibitors.3 In vivo studies are a key step mandated by the FDA before human testing can be underway. There are many different types of animal models, one of the more common being the mouse. However, studies have shown that crucial genetic, molecular, immunologic, and cellular differences between...
humans and mice prevent animal models from serving as effective means to seek for a cancer cure. Among 4,000+ genes in humans and mice, researchers found that transcription factor binding sites differed between the species in 41 to 89% of cases. In order to circumvent these costly and inefficient animal studies, within the past decade the FDA has approved phase 0 studies in oncology. In a phase 0 study, a small number of human volunteers are exposed to a new drug at a microdose compared to the starting dose in a phase I study. There is no therapeutic intent, rather the goal is to quickly determine the pharmacokinetic and pharmacodynamic profiles of the drug in humans. However, owing to the low doses administered, the limited number of humans treated and the reduced risk of toxicity, the phase 0 strategy would require fewer preclinical in vitro and in vivo studies than a typical phase I trial in a cost-efficient and more time-efficient manner.

Studies published in the 1990s described the apparent upregulation of transforming growth factor β (TGF-β) and its protein receptor tyrosine kinase, epidermal growth factor (EGFR) in fresh tissue specimen of patients with HNSCC compared to normal individuals. The increased messenger RNA (mRNA) expression of EGFR plays a direct role in oncogenesis for HNSCC and other epithelial tumors such as breast, lung, colon, and prostate cancer. High levels of EGFR, which have been seen in approximately 90% of SCCs of the head and neck, have been shown to correlate with worse clinical outcome, decreased response to radiotherapy (RT), and increased locoregional recurrence following definitive RT. C225, a chimeric antibody derived from the 225 murine antibody, is a highly specific monoclonal antibody that binds specifically to the human EGFR with an affinity equal to its ligand, competes with the ligand for binding, and blocks activation of the receptor tyrosine kinase. It was chimerized to the human immunoglobulin G1 (IgG1) constant region to avoid human anti-mouse antibody production. Fig. 28.2 outlines the EGFR pathway and the mechanism of action of C225. Further in vitro studies demonstrated that the treatment of the human epidermoid carcinoma A431 cell line with the C225 monoclonal anti-EGFR antibody resulted in a dose-dependent inhibition of vascular endothelial growth factor (VEGF) expression at both the mRNA and protein levels. Significantly, this decline in VEGF was not restricted to in vitro treatments; four injections of C225 antibody into nude mice with an established A431 human epidermoid carcinoma xenograft resulted in an obvious downregulation of VEGF expression, which accompanied tumor growth inhibition. Finally, the effect of C225 on radiosensitivity was studied in mice and showed that C225 augments in vivo tumor response of SCC to radiation. This overwhelming tumor response prompted C225 to become known as cetuximab and enter the next phase of drug development.

28.2.2 Phase I Clinical Trial

Once a drug is sufficiently tested in animal models with promising results, the drug is deemed ready to embark on a clinical trial. The goal of a phase I study is to determine the safety and dosage of the drug. Enrolled subjects can either be healthy volunteers or cancer patients. Usually, this is a small group of about 20 to 100 persons. Study investigators must determine the initial dose, dosing schedule, anticipated side effects, and toxicity based on preclinical studies. Except in phase 0 studies, this is usually the first time that a drug is administered to a
human. As such, various dosing escalation algorithms have been proposed in order to maximize quickly achieving the maximal tolerated dose (MTD) while minimizing toxicity. Typically, the final recommended dose tends to be one dose lower than the MTD. Phase I clinical trials tend to be more subjective than phase II or III trials, as investigators must decide which dose should be the starting dose, which doses should be given to the next cohort of subjects, and when to stop. More recently, adaptive designs such as bayesian methods have demonstrated scientific advantages over conventional designs. They can estimate the target dose more accurately. Bayesian methods based on two-parameter models can estimate the whole dose–response relationship curve optimally. Modified continual reassessment method (CRM) and other bayesian methods have been used in real phase I trials. They are good evidence that new approaches are achievable when statisticians and clinicians work together efficiently.\(^\text{11}\)

Phase I studies of cetuximab administered alone or in combination with cisplatin in patients with stage III or IV epithelial tumors with EGFR overexpression were published in the early 2000s.\(^\text{13}\) Malignancies including head and neck, prostate, renal cell, non–small-cell lung cancer, ovarian, pancreas, breast, and bladder were represented. The first study investigated a single IV dose with a dose escalation protocol in groups of three. A total of 13 patients were included in the study. In the second study, patients received weekly IV cetuximab for 4 weeks according to a dose escalation schedule (17 patients). Finally in the third study, patients received IV cetuximab for 4 weeks according to a dose escalation schedule in addition to cisplatin (22 patients). Sixteen of the 22 patients in this group had HNSCC. Results from these studies calculated the recommended dose to be 200 mg/m\(^2\) as the dose whereby complete saturation of antibody clearance was observed. In addition, cetuximab pharmacokinetics were not altered by coadministration of cisplatin. Observed side effects included skin toxicity in the development of an acne-like rash, which was found to be dose-related. Grade 3 or higher cetuximab-related toxicity episodes were rare (five episodes), and all but two occurred when cetuximab was combined with cisplatin at 100 mg/m\(^2\). Grade 3/4 adverse events using cetuximab and cisplatin occurred with doses of cetuximab that seemed to be safe when given as multiple injections without chemotherapy. The cisplatin dose was then reduced to 60 mg/m\(^2\), and the planned cetuximab dose escalation proceeded starting at the 5 mg/m\(^2\) dose level; after this modification, the study was completed without reaching the MTD.\(^\text{12}\)

Given the correlation of EGFR expression with poor prognosis and the fact that preclinical studies identified cetuximab as a radiosensitizer, a phase I study was undertaken to assess the interaction of cetuximab and RT in patients with locally advanced, unresectable HNSCC.\(^\text{13}\) Patients were enrolled sequentially onto five treatment groups that comprised of at least three assessable patients in each group, with all patients at the preceding dose level having received at least two doses of cetuximab. Dose escalation proceeded in the absence of a study drug-related dose-limited toxicity. If, at any dose level, one of the three patients experienced a dose-limiting toxicity (DLT), two additional patients were to be enrolled at that dose level. RT was begun on day 8 and continued for a total of 76.8 Gy at 7 weeks. Results from the study showed that the treatment was well tolerated with the most common side effect being an acneform skin rash. This was felt to represent the antibody’s interaction with EGFR. The authors concluded that cetuximab can be administered safely for prolonged periods of time in combination with RT. The maximum-tolerated dose and recommended phase II/III dose, based on the protocol design of our study, is a loading dose of 400 to 500 mg/m\(^2\) and a maintenance weekly dose of 250 mg/m\(^2\).\(^\text{13}\)

The outcomes from these studies determined a maximum-tolerated dose for cetuximab approved for human use. Though not the focus of these phase I clinical studies, many of the patients enrolled either showed a clinical response to cetuximab in terms of tumor regression or showed stabilization of the burden of disease. Cetuximab was approved for further study with a phase II clinical trial. Approximately 70% of drugs approved for a phase I clinical trial move to the next phase.\(^\text{14}\)

### 28.2.3 Phase II Clinical Trial

Once a drug is approved for a phase II trial, the focus shifts to determining efficacy and evaluating side effects. Up to several
hundred patients afflicted with the disease studied will be enrolled in the study, and the typical study duration is typically several months up to 2 years.14

Initial phase II studies in head and neck cancer determined the safety and efficacy of cetuximab in addition to cisplatin chemotherapy for the treatment of refractory metastatic or recurrent HNSCC. In one study, patients with documented recurrence or progressive disease within 3 months of platinum-based therapy were eligible.15 After an initial enrollment of 187 patients, 131 patients went on to receive cisplatin plus weekly cetuximab therapy after an initial loading dose based on phase I data. Results showed that of the 51 patients with stable disease, 9 (18%) achieved major tumor response, with 39 patients (76%) considered to achieve some measure of disease control. The median overall survival time for the stable disease cohort was 11.7 months. There were 54 patients with a clear demonstration of disease progression after chemotherapy administered within 90 days before treatment. In this group, only 3 patients (6%) achieved a partial response and another 25 patients (46%) had stable disease.15 The most common nonhematologic toxicity generally associated with cetuximab was rash, which occurred in 70% of patients. The most common grade III and IV cisplatin toxicities were myelosuppression and nephrotoxicity. The most common hematologic toxicity was anemia, which occurred in 92% of patients.15

Given the overall poor survival in patients with unresectable head and neck cancer, in 2014, the Eastern Cooperative Oncology Group published a phase II clinical trial investigating cetuximab plus cisplatin and radiation in unresectable, locally advanced head and neck cancer.16 Among 60 eligible patients, ultimately 44 patients received a cetuximab loading dose followed by radiation and three courses of cisplatin with weekly cetuximab, followed by maintenance cetuximab therapy. About 39% received at least 6 months of maintenance; 14% received a full year of maintenance therapy. Of the 60 analyzable patients, 39 (65%) were still alive more than 2 years after registration, and the 2-year progression-free survival rate was 47%.16

In the colorectal cancer (CRC) literature, phase II clinical trials of cetuximab given alone for chemotherapy refractory CRC showed a favorable clinical response rate in tumors expressing EGFR.17 Combination trials of capcitabine and oxaliplatin (CAPOX) plus cetuximab in patients with metastatic colorectal cancer who progressed after oxaliplatin-based chemotherapy showed an even higher overall response rate, time to tumor progression, and response rate than cetuximab alone.18

The acneiform rash was the most documented toxicity observed with cetuximab among all tumor types. It was noted to be perhaps a clinical predictor of overall survival which was better elucidated in phase III studies.19 Overall, only about 33% of drugs in phase II clinical trials move on to phase III clinical trials.14

### 28.2.4 Phase III Clinical Trial

A phase III clinical trial consists of a large cohort of patients receiving treatment for a particular disease. Typically, several hundreds to thousands of patients are enrolled in the study. The goal of a phase III clinical trial is to compare the novel treatment to the current standard of care in terms of efficacy and adverse effects. Ideally, patients are randomized to either treatment group with the best studies conducted in a double-blind fashion.

A study published in 2010 reviewed 5-year data from a randomized phase III clinical trial investigating RT with or without cetuximab for patients with locally advanced HNSCC.7 Initially, 424 patients were assessed for eligibility and 213 were randomized to radiation alone, whereas 211 patients were randomized to radiation plus cetuximab. There were three different RT regimens, each delivering a total of 70 to 72 Gy. For patients who received concomitant cetuximab with radiation, after an initial loading dose of 400 mg/m², patients received 7-weekly infusions of 250 mg/m² of cetuximab during radiation. Results showed that median overall survival in the RT alone group was 29 months, compared with 49 months in the radiation plus cetuximab group, while 5-year overall survival was 36.4 and 45.6%, respectively (p = 0.018).7 Of 211 patients in the cetuximab group, 174 developed an acneiform rash, 127 patients had a prominent rash, and the remaining 81 patients had mild rash or none. The study inferred that it is possible that the acneiform rash is a biomarker of an immunologic response that is conducive for optimal outcome.19 Patients with prominent rash had more than 2.5 times longer overall survival than did patients with mild rash.7

Other phase III clinical trials incorporated cetuximab with preexisting treatment paradigms in metastatic CRC as well as non–small-cell lung cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) trial investigated cetuximab plus irinotecan versus irinotecan alone for patients with metastatic colorectal cancer who had failed first-line fluoropyrimidine and oxaliplatin therapy. The overall response rate as well as progression-free survival was significantly longer in the cetuximab plus irinotecan group although ultimately overall survival was comparable.20 Finally, the FIT Long-Term Extension (FLEX) trial studied cetuximab plus chemotherapy versus chemotherapy alone in patients with advanced non–small-cell lung cancer. In the group treated with cetuximab, overall survival and response rates were significantly improved compared to the chemotherapy alone arm of the study.21

One of the common themes across all of these phase III clinical trials is that the development of a skin rash in patients who were treated with cetuximab correlated with improved survival and tumor response rates. It was also noted that the severity of the skin rash was an independent prognostic indicator of survival.

In summary, approximately 25 to 30% of drugs which reach the level of a phase III trial move on to receive regulatory approval.14

### 28.2.5 Phase IV Clinical Trial

A phase IV clinical study is performed on a drug after it has received FDA approval. The goal of this phase of study is to continue studying potential long-term side effects in patients receiving the drug. These are typically long-term, large-scale observational studies with thousands of patients enrolled. A review of currently registered clinical trials showed that there is only one ongoing phase IV clinical trial involving cetuximab in head and neck cancer patients.7 In addition, after a drug gains initial regulatory approval in a given disease, it is common for additional phase II/phase III trials to be conducted to broaden the indications for the use of this drug. For example,
in many cancer types, including HNSCC, most trials of new therapeutics are targeted toward patients with recurrent or metastatic disease, and later trials then assess the use of the drug in first-line therapy.

### 28.2.6 Ongoing Clinical Trials Involving Cetuximab in Head and Neck Cancer

Postoperative RT in stage III/IV and selected stage II HNSCC is currently the standard of care as described by Forastiere in 2001. Several studies have investigated the role of concurrent adjuvant cisplatin and RT for patients with positive margins and/or presence of extracapsular extension. The study led by Cooper in 2004 showed significantly improved locoregional control (LRC) and disease-free survival (DFS) but not overall survival, compared with postoperative radiation therapy (PORT) alone. Also, administration of high-dose cetuximab was associated with severe toxicity including dysphagia, neuropathy, and hearing loss. As such, multiple series of data report a rate of locoregional failure between 15 and 35% for these patients, despite adjuvant RT.

RTOG 0920 is an ongoing prospective randomized phase III clinical trial by the Radiation Treatment Oncology Group headed by Machtay at Case Western Reserve University. The goal of the study is to investigate the role of adjuvant RT alone versus adjuvant RT plus cetuximab in patients with locally advanced, resected head and neck cancer. The hypothesis is that patients treated with RT plus cetuximab will have significantly improved DFS and LRC. Patients with oral cavity, larynx, and both p16+ and p16− oropharynx SCC are eligible to enroll with a goal enrollment of 700 patients. Patients are initially stratified based on degree of EGFR tissue expression from samples obtained prior to randomization. Once enrolled in the study, patients are then randomized to one of two research arms. The first is postoperative radiation alone in 2-Gy fractions for a total of 60 Gy. In the second arm of the study, patients receive radiation in 2-Gy fractions for a total of 60 Gy as well as cetuximab. The drug regimen is an initial dose of 400 mg/m², followed by weekly infusions of 250 mg/m² for 6 weeks during radiation, plus 4 weeks of cetuximab at 250 mg/m² post-RT. The results from this study will provide valuable information in the hopes that cetuximab will cause less toxicity than cisplatin and improve overall DFS, LRC, and overall survival compared to RT alone or RT plus cisplatin.

### 28.3 Newer Innovative Trial Designs

The clinical trial process as described previously is very expensive and time consuming. Large populations of patients are needed to conduct a study, as well as infrastructure and financial resources resulting in high drug failure rates. As we come to better understand specific tumor biology and genetic targets, there is a need to streamline the drug development process. As a result, new methodological strategies have been developed, such as basket and umbrella trials.

#### 28.3.1 Basket Trials

This type of study design enrolls patients with a variety of tumor types but with a common molecular alteration (Fig. 28.3). This allows researchers to separately analyze the responses of patients as each tumor type can be put in one cohort, and assess the impact of the drug on all of the patients as one group. If one group shows a good response, the group is expanded to immediately assess whether others could benefit from the new therapy. If another group does not show evidence of effectiveness, this group may be closed and the other cohort can continue the recruitment. There are three main types of basket trials: one drug, several tumor types; one drug, one molecular target, several tumor types; and one drug, several molecular targets, several tumor types. (Fig. 28.3a provides a schematic of the study design for a basket trial.

A basket trial published in the *New England Journal of Medicine* in 2015 investigated specific cancer groups with *BRAF* V600 mutation-positive nonmelanoma cancers. A total of 122 patients were enrolled in the study, and the cancers represented included colorectal, non–small-cell, Langerhans’ cell histiocytosis, primary brain tumors, cholangiocarcinoma, anaplastic thyroid cancer, and multiple myeloma. The study drug was vemurafenib, a selective oral inhibitor of the *BRAF* V600 kinase associated with improved survival among patients with *BRAF* V600E mutation-positive metastatic melanoma. Patients in the colorectal group received vemurafenib plus cetuximab therapy. Results showed that vemurafenib had beneficial response rate and progression-free survival in some but not all tumors with a *BRAF* V600 mutation, mainly non–small-cell lung cancer, and in Erdheim–Chester disease and Langerhans’ cell histiocytosis. This study allowed multiple different tumor types with the same mutation to be studied concurrently and showed that each tumor has different vemurafenib activity despite the presence of the same genetic mutation.

#### 28.3.2 Umbrella Trials

Whereas a basket trial tests a single agent against multiple tumors with the same molecular target, an umbrella trial is designed to test the impact of different drugs on different mutations in a single type of cancer, on the basis of a centralized molecular portrait performed after obtaining informed consent: one disease, several molecular subtypes, several therapies. (Fig. 28.3b depicts the study setup for an umbrella trial.

An example of an umbrella trial is the National Lung Matrix Trial which investigated several different drugs targeted at specific mutational targets. A total of 20 molecular cohorts were randomized to 6 different treatment arms with the primary end points of response rate and progression-free survival. The trial is currently ongoing across 18 centers in the United Kingdom. One of the advantages of this study is that the trial allows for new arms to be entered via substantial amendment. Rather than starting from scratch for each new therapeutic strategy, a new therapy can be added into an existing umbrella trial if a review panel is convinced of the strength of the preclinical data supporting the clinical combination of the biomarker and targeted agent. This will significantly reduce the time from concept to clinical study.
Fig. 28.3 (a) Basket trial design. In this trial, multiple different cancer types (represented by different colors) harbor a variety of mutations (represented as shapes). Mutational profiling is used to identify the tumors harboring the mutation of interest, and the cancers harboring that mutation are enrolled and treated with the drug of interest. (b) Umbrella trial design. In this trial, a single cancer type (i.e., HNSCC) harbors multiple mutational phenotypes (represented as different shapes). Mutational analysis is performed on each patient enrolled in the trial, and the treatment arm is assigned based on the mutational profile of a patient’s cancer.
28.4 Immunotherapy: The Next Round of Innovation in Head and Neck Cancer

Despite the success of targeted therapies in some forms of cancer, recent data from high-throughput exome sequencing projects on head and neck cancer have highlighted the extreme heterogeneity of HNSCC. Aside from p53 inhibition, there is no other genetic alteration that occurs in more than 20 to 25% of HNSCC, and most genetic changes occur in only a small number of cases. Thus, it is unlikely that there will be any single targeted therapy that directly inhibits HNSCC growth. While individualized cancer genomics and personalized medicine may be one means to address this heterogeneity, an alternative method may be to harness the immune system’s endogenous antitumor properties to target HNSCC.

It is well established that immunodeficiency and immunosuppression greatly increase the risk of cancer development, and it is hypothesized that immune surveillance prevents cancer development. Although the concept of immune surveillance is more than 50 years old, only recently has immune modulation moved into the mainstream of cancer treatment. Immune infiltrates have long been recognized to be a common feature of many malignancies, including head and neck cancer. These immune cells are generally believed to be reacting to the “foreign” antigens produced by mutated cancer cells; however, evasion of this immune response is critical to tumor growth and progression. Central to this immune response is T-cell activation, primarily cytotoxic T cells. The cytotoxic T-cell response is driven by two primary signals: recognition of antigen associated with the major histocompatibility (MHC) on antigen-presenting cells, and costimulatory signaling through T-cell receptor interactions between the T cell and the antigen-presenting cell. This costimulatory signal is subject to multiple “checkpoints” that regulate this process and may be exploited by tumor cells to downregulate the immune response (> Fig. 28.4). Novel treatments targeting these signaling events have already demonstrated significant efficacy in the treatment of melanoma, and have demonstrated promise in the treatment of HNSCC.

28.4.1 Immunotherapy in Melanoma

Although a comprehensive review of melanoma immunotherapy is outside the scope of this chapter, a brief overview of this subject is useful, as many of the therapies pioneered in melanoma are now being applied to HNSCC. Melanoma has long been recognized to have a complex interaction with the immune system. Over 20 years ago, interferon-α-2b (IFN-α-2b) was recognized as an important adjuvant therapy in melanoma treatment, which demonstrated an improvement in DFS and overall survival. Additional studies confirmed that IFN-α-2b increased DFS, although not necessarily overall survival; furthermore, this treatment carries significant toxicity and relatively modest benefit. Thus, its use remained somewhat limited, although it has continued primarily due to a lack of viable alternatives.

Until recently, high-dose interleukin 2 (IL-2) was the only other FDA-approved treatment for advanced melanoma. This
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Treatment is associated with a 16 to 23% response rate, and 5 to 10% of patients achieve a durable response that can last for many years. However, this is a highly toxic therapy that induces a profound capillary leak syndrome, with associated hypotension/shock, renal failure, and need for massive fluid resuscitation, requiring it to be administered in an inpatient intensive care setting. This toxicity and low response rate has limited its application to only a few select centers. Adoptive T-cell transfer, which involves harvesting and expansion of tumor-infiltrating lymphocytes, followed by administration with IL-2 after lymphodepleting chemotherapy, has also shown promise, with remissions observed in up to 40% of patients, but this therapy remains experimental, expensive, and extremely time-consuming.

Over the past few decades, increasing understanding of T-cell regulation revealed the presence of immune activation checkpoints critical to the activation of T-cell response. Two checkpoints in particular have recently gained substantial attention as therapeutic targets: CTL antigen 4 (CTLA4) and programmed death 1 (PD-1) (Fig. 28.4). CTLA4 is expressed on T cells and interacts with B7-1 and B7-2, costimulatory molecules on the antigen-presenting cell. Given its potent role in modulation of the immune response, monoclonal antibodies have been developed targeting this molecule. The first anti-CTLA4 agent to gain FDA approval is ipilimumab, which was approved in March 2011. Multiple phase III studies of ipilimumab alone or in combination with other therapeutic agents have demonstrated a consistent survival advantage with the use of ipilimumab. For example, a large-scale randomized phase III trial of ipilimumab + glycoprotein 100 vaccine for metastatic melanoma after previous systemic treatment showed a significant increase in overall survival to 10.1 months with ipilimumab alone (95% confidence interval [CI]: 8.3–13.8) or 10 months with ipilimumab + gp100 vaccine (95% CI: 8.5–11.5) versus 6.4 months with gp100 alone (95% CI: 5.5–8.7). Numerous clinical trials have been performed or are ongoing with ipilimumab in combination with other agents, such as granulocyte macrophage colony-stimulating factor (GM-CSF), bevacizumab, and other agents for patients with recurrent/metastatic melanoma.

Additionally, ipilimumab has shown efficacy in an adjuvant setting. In a randomized, placebo-controlled, double blind phase III trial of patients with stage III melanoma after surgery, ipilimumab increased recurrence-free survival to 26.1 months (95% CI: 19.3–39.3) from 17.1 months with placebo (95% CI: 13.4–21.6). Based on these findings, ipilimumab gained additional FDA approval for use in the adjuvant setting for patients with stage III melanoma. However, this drug does have the potential for serious toxicities, largely related to excessive immune activation. Severe (grade III–IV) gastrointestinal, hepatic, and endocrine autoimmune complications can occur with ipilimumab; approximately 15–20% of patients develop severe colitis, and adverse side effects may limit treatment in up to 50% of patients.

The other major immune checkpoint to be targeted in melanoma treatment is the interaction between PD-1 (expressed on T cells) and PD-L1 (expressed on macrophages and tumor cells). Monoclonal antibodies targeting each of these molecules have been developed. Pembrolizumab and nivolumab are both PD-L1 inhibitors that were approved by the FDA in late 2014 for the treatment of metastatic/unresectable melanoma after failure of ipilimumab. Although several studies demonstrated the efficacy of these medications, perhaps the most impressive is a large, randomized, controlled, phase III study of two different dosing regimens of pembrolizumab versus ipilimumab. This demonstrated approximately 6-month progression-free survival rates of approximately 47% for either pembrolizumab dose versus 26.5% for ipilimumab, with superior 12-month survival and overall response rates for pembrolizumab as well. Furthermore, pembrolizumab demonstrated an improved safety profile compared to ipilimumab, with grade III to V adverse events occurring in 10 to 13% of pembrolizumab patients and 20% of ipilimumab patients. Based on this data and other studies demonstrating the superiority of pembrolizumab to ipilimumab, the indications for pembrolizumab were expanded to include first-line therapy for unresectable melanoma. The combination of ipilimumab and nivolumab has also been approved for the treatment of metastatic/unresectable melanoma with wild-type BRAF, based on data demonstrating an improvement in progression-free survival to 11.5 months with combination therapy versus 6.9 months with nivolumab alone and 2.9 months for ipilimumab alone. Currently, phase III trials are ongoing to assess the efficacy of these medications in the adjuvant setting. Several other agents targeting either PD-1 or PD-L1 are also in various stages of development for the treatment of melanoma.

28.4.2 Immunotherapy in Head and Neck Cancer

Based on the successes of anti-PD-1 agents in melanoma, a proliferation of trials for new indications is occurring, which will likely bring these agents into more widespread use among multiple other types of cancer. Nivolumab currently also has approved indications for use in metastatic non–small-cell lung cancer and renal cell cancer, while pembrolizumab has approval for use in metastatic non–small-cell lung cancer. Head and neck cancer is not far behind.

To date, there is little published data utilizing either CTLA4 or PD-1 antibodies. A phase Ib trial of the safety and efficacy of pembrolizumab for recurrent/metastatic head and neck cancer with confirmed PD-L1 expression has been reported (KEYNOTE-012). This demonstrated an overall response rate of 20%, with a response duration of 8 to 41 weeks. However, multiple larger-scale phase III trials are nearing completion, and the first results have been reported in abstract form. Most importantly, in April 2016, the first results from the CheckMate-141 trial were reported, a phase III randomized, open-label trial of patients with recurrent/metastatic HNSCC after failure of platinum therapy, testing nivolumab versus investigator’s choice of therapy (methotrexate, docetaxel, or cetuximab). Patients treated with nivolumab demonstrated increased overall survival to a median of 7.5 months compared to 5.1 months on investigator’s choice, with a 1-year survival rate of 36% on nivolumab versus 16.6% on investigator’s choice. Around this same time, the results of the KEYNOTE-012 expansion cohort study were reported, detailing longer follow-up data for recurrent/metastatic HNSCC treated with pembrolizumab. This demonstrated a response rate of 25% with durable remissions, regardless of tumor human papillomavirus (HPV) status. An additional randomized phase III trial of pembrolizumab versus investigator’s choice for...
recurrent/metastatic HNSCC (KEYNOTE-40) has completed enrollment, but results have not yet been reported. Based on these studies, it is widely expected that FDA approval for the use of these PD-1 inhibitors in recurrent/metastatic head and neck cancer will be coming soon.

A wide range of studies for additional indications for PD-1 inhibitors in HNSCC are currently underway. Pembrolizumab is currently being investigated for use as a first-line agent for recurrent/metastatic disease (KEYNOTE-48), and several trials are being set up to examine its use in either the definitive chemoradiation setting or in the neoadjuvant/adjuvant setting after surgical resection. Similarly, nivolumab is also moving toward first-line therapy. A large phase III randomized trial of cisplatin-based chemoradiation +/− nivolumab for previously untreated, locally advanced HNSCC is currently in development (RTOG 3504). Although these trials will require several years to complete, it is quite possible that anti-PD-1 therapy will become a common treatment for HNSCC.

Although these PD-1 inhibitors are generating excitement as a potential novel means of treating head and neck cancer, the fact remains that only a subset of patients show significant benefit with these medications in current trials. Thus, personalized immunotherapy, in combination with personalized anti-tumor agents, may be critical to successful treatment of most head and neck cancer. For example, the current phase II trials (HAWK, CONDOR, and EAGLE) investigating durvalumab (MEDI4736, AstraZenica), a PD-L1 inhibitor, stratify patients based on tumor PD-L1 expression status, indicating patients for treatment is durvalumab and/or tremelimumab, a CTLA4 inhibitor. In multiple tumor types, there appear to be inflamed and noninflamed tumor phenotypes, characterized by the amount and makeup of immune cell infiltrates into the tumor tissue.53, 54 While targeting immune checkpoints such as PD-1 and CTLA4 in the inflamed phenotype appears to be a potentially successful strategy, management of the noninflamed phenotype is more problematic. In short, the immune system must be brought to the tumor and primed first, before it may be activated to effectively attack the tumor cells. Tumor vaccination strategies may be one means to achieve this aim. Priming the immune system to react to mutated p53 proteins frequently seen in HNSCC is one potential strategy. In a small phase 1b trial, patients were treated with injections of dendritic cells pulsed with p53 peptides.55 The 2-year DFS was 88%, and the majority of patients demonstrated increased frequencies of p53-specific T cells. Alternatively, HPV proteins may be a potential target for cancer vaccine therapy. Although only small feasibility studies have been performed in head and neck cancer,56 larger studies using vaccines to E6 and E7 in cervical cancer have shown promising results.57 Several studies of similar vaccines are currently underway in a variety of settings, including both advanced disease and in preoperative, window-of-opportunity studies.

In summary, there is currently a rapid growth in interest in immunotherapy for HNSCC. Several novel therapeutic agents are in development, with a proliferation of trials investigating the utility and indications for various immunomodulatory strategies. The next several years promises to bring significant change to the treatment of head and neck cancer, with immunotherapy likely to become a fourth major modality of treatment, alongside surgery, radiation, and traditional chemotherapy.

28.5 Conclusion

The achievements within the past decade will continue to improve outcomes for patients with head and neck cancer and melanoma. As innovations in our understanding of specific tumor targets continue to evolve, the drug development process will need to be further streamlined while maintaining the safety of patients. Newer adaptive design methods will likely have an expanded role to allow for more central testing of multiple patients with specific mutations. Ultimately, the goal remains to individualize patient treatment in order to provide the maximum therapeutic benefit while minimizing side effects. The next decade will continue to see major drug development as more specific targets are elucidated.

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Drug Development in the 21st Century: Monoclonal Antibodies and Immunotherapy


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The Vessel-Depleted Neck: Microvascular Reconstruction

29.1 Introduction

Microvascular reconstruction has revolutionized the approach to head and neck cancer treatment, with success of microvascular free tissue transfer reported at over 95%. However, several factors influence the success of the reconstruction, including the patient’s nutritional status and general health, as well as the surgeon’s training, experience, resources, and techniques employed. Perhaps one of the most critical factors, though, is a prior history of chemotherapy, radiation, and/or surgery, which alters the native anatomy and associated vasculature, and often affects the success of the reconstruction.

Recurrent disease, second primaries, and delayed wound breakdown remain a persistent and even growing problem. It is common to encounter patients who have been exposed to chemoradiation and perhaps even undergone several microvascular reconstructions, leaving their surgical bed devoid of vessels appropriate for microvascular anastomosis. Even though a vessel may not have been resected, it may still be rendered inadequate for anastomosis due to the significant fibrosis and early atherosclerosis induced by radiation. The situation in which the usual vessels utilized for microsurgery have been eliminated has become referred to as “the vessel-depleted neck.”

Strictly speaking, this term refers to patients lacking an adequate internal jugular vein, external jugular vein, and multiple branches of the external carotid artery (i.e., the superior thyroid, lingual, and facial) for microsurgical reconstruction. As the vessel-depleted neck has become a more common problem, strategies have been proposed identifying vessels outside of the previous surgical and radiation field for microvascular anastomosis. The microvascular surgeon should understand the techniques and vascular options available to successfully overcome these challenges presented by patients with vessel-depleted necks.

Note

Even though a vessel may not have been resected, it may still be rendered inadequate for anastomosis due to the significant fibrosis and early atherosclerosis induced by radiation.

29.2 Vascular Considerations

The selection of appropriate recipient vessels is one of the most important aspects determining the success of microvascular reconstruction (Fig. 29.1). In the head and neck, veins usually accompany their arterial counterparts; however, venous anatomy tends to be much more variable and less reliable. In microvascular surgery, veins are less tolerant of size mismatch, and in the previously irradiated neck, venous atherosclerosis and fibrosis may be encountered. Thus, in the vessel-depleted neck, choosing the appropriate vein for anastomosis can be the most challenging aspect.

Flap failure is most often due to venous thrombosis, and the signs and symptoms of venous thrombosis are less easily recognized, frequently leading to late diagnosis and flap failure. In the head and neck, the internal and external jugular veins are the standard vessels used. These vessels reliably provide adequate diameter for anastomosis, preventing size mismatch, which is known to affect thrombosis rates. Many surgeons prefer to use the internal jugular vein because of the reported statistically significant higher rates of venous thrombosis in the external jugular vein.

Note

Flap failure is most often due to venous thrombosis, and the signs and symptoms of venous thrombosis are less easily recognized, frequently leading to late diagnosis and flap failure.

However, often the internal and external jugular veins have been sacrificed or manipulated during the ablative portion of the surgery, rendering them useless. Even if the vessels are present, they may lack sufficient size or patency for anastomosis due to the radiation-induced intimal fibrosis and atherosclerosis. After a prior neck dissection or neoadjuvant chemoradiation, studies have demonstrated that 16% of patients will lack an adequate internal or external jugular vein for microvascular anastomosis. Furthermore, even if the veins are present and of adequate caliber, transient thrombosis of the internal jugular occurs in up to 24% of patients after neck dissection, which may affect the flap viability.

In patients who have only undergone unilateral neck surgery or radiation, contralateral neck vessels may be utilized. However, this technique often necessitates use of a vein graft, which has consistently poorer outcomes due to the presence of two anastomoses, the pedicle length required, and the final geometry of the vessels oriented horizontally along the axis of the neck. In fact, some retrospective studies have reported the success of vein grafts to be as low as 70%. For these reasons, the choice of venous pedicle and anastomosis is critical to the success or failure of the microvascular reconstruction.
29.3 Transverse Cervical Vessels

Even in the previously untreated neck, the transverse cervical vessels are frequently used for microvascular reconstruction, and as such, are considered the first option when approaching the vessel-depleted neck. Given their origination in the inferior neck, they are typically outside the previous treatment field.

Traditional anatomical teaching describes the transverse cervical artery originating from the thyrocervical trunk (77.5% of patients); however, it can also be found arising directly from the subclavian artery (20.8%) or internal mammary artery (1.7%). The corresponding vein can be found draining into either the external jugular or the subclavian vein. Starting lateral to the insertion of the clavicular head of the sternocleidomastoid (SCM), these vessels can be traced across the posterior triangle of the neck in a posterolateral direction. Along its course, the transverse cervical artery travels on top of the anterior scalene, under the inferior belly of the omohyoid, and over or through the brachial plexus on its path toward the trapezius muscle. At the trapezius muscle, the artery then divides into two main branches: an ascending, superficial branch and a descending, deep branch. The transverse cervical vein has a slightly more variable course and can be found running deep (75%) or superficial (25%) to the omohyoid before continuing on its path toward the trapezius muscle.

Preoperatively, the transverse cervical artery can sometimes be palpated in the supraclavicular region, just lateral to the insertion of the SCM on the clavicle. This localization is sometimes made easier in a previously operated neck, in which the posterior triangle fat pad/lymph nodes have been dissected. However, in the previously untreated neck, a Doppler probe can be employed preoperatively and during dissection to assist in isolating the vessels. The dissection is started with a small horizontal incision made 2 cm above and parallel to the clavicle, just lateral to the SCM. If a neck dissection incision is part of the ablative portion of surgery, then an inferior limb can be created and directed toward the midclavicle to gain exposure instead. Once the incision is made, the inferior belly of the omohyoid is identified superior to the clavicle and lateral to the SCM. With these three structures (SCM, omohyoid, and clavicle) identified, the loose fatty tissue contained within this triangular space is carefully explored using blunt dissection to isolate the artery and vein. If a neck dissection is already being performed, the SCM may be retracted laterally to identify the vessels slightly posterolateral to the SCM just above the clavicle. Once the vessels are found, dissection proceeds posterolaterally, harvesting as much length as possible, while still ensuring the vessels are of appropriate caliber for anastomosis.
dissected distally, the quality of the vessel and the arterial pressure typically remains excellent. Once an adequate length of the vessels is harvested, care should be taken to free up any attachments near their takeoff that may lead to kinking of the final anastomosis. Of note, several important structures are encountered during the dissection, most notably the external jugular vein, the brachial plexus, and the thoracic duct in the left neck. Care must be taken to identify and preserve these structures.

**Note**

During the dissection of the transverse cervical vessels, the external jugular vein, the brachial plexus, and the thoracic duct may be encountered. Small cutaneous sensory nerves may also be encountered; however, they can often be retracted without sacrificing the nerve branches.

The distance from the transverse cervical vessels and the mandibular angle is generally less than 10 cm, which is well within the reach for most flap pedicles. To achieve correct orientation, the vessels are transposed 90 degrees and brought into the upper neck through a subcutaneous tunnel. Often, arranging the pedicle on top of the SCM makes for a technically easier anastomosis; a notch may be cut into the lateral border of the SCM to create a stable resting place for the vascular pedicle.

The transverse cervical vessels have become a favored vessel of choice for many microvascular surgeons. Harvesting the vessels is straightforward, with exploration and dissection generally taking no more than 15 minutes. Furthermore, the thyrocervical trunk is less likely to be involved in the ablative portion of the surgery, and its location at the periphery of the radiation field significantly decreases postradiation changes to the vasculature. Finally, after transposing the vessels 90 degrees relative to their native takeoff, they lie in the midportion of the neck, facilitating ease of anastomosis. This transposition places the vessels along the vertical axis of the neck, allowing for a straight course from the transverse cervical vessels to the pedicle of the flap and reducing the risk of postoperative kinking, tension, stretching, or other manipulation with neck movement.

Although the transverse cervical vessels are considered the first-line option in the vessel-depleted neck, they are not without limitations. In some patients, the vessels may naturally be small, or the vein virtually absent. Occasionally, due to extensive previous surgery, the vessels may not have been preserved. Also, this region is sometimes not completely outside of the...
radiation field, making the vessels susceptible to fibrosis, scarring, and postradiation arteriosclerosis. A case series by Yu investigating the use of the transverse cervical vessels in the vessel-depleted neck demonstrated that the vessels could be successfully used for anastomosis in 92% of patients. However, in 23% of the patients, contralateral vessels had to be explored and used for the anastomosis, and in 8% of the cases, the vessels were either absent due to a previous ablative surgery or were too small for anastomosis (< 2 mm). Lastly, harvesting these vessels eliminates the possible future use of an ipsilateral lower trapezius or upper trapezius island flap.

Note
The transverse cervical vessels may be absent in up to 8% of patients requiring alternative approaches. In up to a quarter of patients, the vessels may be diminutive to use for microvascular reconstruction.

29.4 Superficial Temporal Vessels

Historically, the superficial temporal vessels were thought to be too small in caliber or too thin walled for reliable free tissue transfer; however, more recent studies have refuted this belief. The superficial temporal vessels are now considered invaluable to the head and neck surgeon, especially given their favorable location for use in the reconstruction of scalp, face, and oral defects.

The superficial temporal artery is the terminal branch of the external carotid artery, originating in the parotid gland before traveling superiorly to the upper face and scalp. After emerging from the parotid gland, the superficial temporal vessels travel over the posterior aspect of the zygomatic arch, approximately 1 to 1.5 cm anterior to the tragus and helix of the auricle. Above the zygomatic arch, the artery splits into two main branches: the anterior frontal branch and the posterior parietal branch. In general, the superficial temporal artery maintains consistent anatomy, though the bifurcation point can be variable, taking place either above the zygomatic arch (60–88%), over the zygomatic arch (4–32%), or rarely, below the zygomatic arch. Although the superficial temporal artery is anatomically predictable, the superficial temporal vein is slightly more variable and can divide into one, two, or three major branches. Given this variability, most microvascular surgeons prefer to perform their free tissue pedicle anastomosis to the main trunk of each vessel, prior to any branching. In general, both the superficial temporal artery and vein tend to maintain adequate caliber for anastomosis: the main trunk of the superficial temporal artery over the zygomatic arch has a mean diameter of 2.73 mm, the frontal branch has a mean diameter of 2.14 mm, and the parietal branch has a mean diameter of 1.81 mm. Likewise, the vein maintains a diameter of 2.1 to 3 mm over the zygomatic arch. However, on rare occasions, it has been noted that dissection must be taken inferiorly to the level of the parotid gland to gain a vein of adequate caliber.

Note
While the superficial temporal artery maintains consistent anatomy, the superficial vein may divide into several small branches and therefore not appropriate for microvascular reconstruction. A preoperative Doppler may be useful to evaluate the reliability of the vessels.

Preoperatively, the superficial temporal artery can readily be palpated or a Doppler may be used in the preauricular region. Once the location has been confirmed, a superficial, vertical, preauricular skin incision is made approximately 1.5 cm lateral to the upper margin of the auricle. Blunt dissection is then carried through the subcutaneous tissue down to the superficial temporal fascia, where the relatively thin-walled superficial temporal vascular bundle is found. The vessels are then dissected free inferiorly to the level of parotid gland, usually at the level of the lobule. At the level of the zygomatic arch, the superficial temporal artery usually gives off a branch called the zygomatico-orbital artery (77.8% of cases), which can be ligated to enhance the mobility of the dissected vessels. The dissection is then continued superiorly into the temporal region depending on the caliber and length of vessel required for anastomosis. Occasionally, the vessels may be of insufficient diameter at or below the zygomatic arch, requiring a small amount of dissection more proximally into the parotid gland. In this situation, care...
must be taken not to damage the frontal branch of the facial nerve. Of note, due to the thin-walled nature of the vessels, some authors recommend use of an operating microscope to dissect out the vessels distally to avoid inadvertent trauma.19

Depending on the location of the defect, the superficial temporal vessels can either maintain their original geometry for scalp and upper face defects, or be rotated in a 90-degree arc for mid-to-lower face or oral reconstruction (Fig. 29.4).19 Given the thin nature of the vessel walls, they are more prone to kinking, and if realignment of the vessels is required, care should be taken to provide a smooth subcutaneous tunnel to the anastomotic site.19 Only a moderate-length pedicle is required for most defects; however, defects of the scalp vertex may require a longer free tissue pedicle for adequate length.

Not only have the superficial temporal vessels been repeatedly used successfully, studies have demonstrated that the facial artery and superficial temporal artery have similar characteristics in the same patient.17,18 Some have suggested that the sheer proximity of the vessel to the defect, either the superficial temporal artery or the facial artery, should be the deciding factor for choosing the recipient vessel.17,18 These authors advocate that the upper face and scalp should rely on the superficial temporal vessels, the lower face should rely on the facial vessels, and the midface should be left to the discretion of the surgeon.18

29.4.1 Superficial Temporal Vein: A Retrograde Venous Outflow Option

The most common recipient veins in the head and neck are the internal and external jugular veins and their branches; however, sometimes even when distal branches of these vessels are available and of adequate caliber, the more proximal portions may undergo thrombosis or severe fibrosis.20 Recent studies have demonstrated the feasibility and utility of retrograde-flow venous drainage, most explicitly in regard to the superficial temporal vein. The anastomosis to the superficial temporal vein is typically performed via anterograde flow, draining from superficial temporal vein to retromandibular vein. However, if necessary, the pedicle of the flap can be attached to the retrograde limb of the superficial temporal vein. In this arrangement, the venous anastomosis takes place at the proximal portion of the vein and the blood flows toward the distal segment, or capillary bed.20,21 Retrograde flow to the superficial temporal vein provides some distinct advantages: its caliber is larger, making size mismatch less likely, and given its geometry, this vein is better suited for anastomosis to flaps in the lower face and neck.20

In the head and neck, this type of drainage is feasible because of the numerous venous interconnections in the head and neck, and the high frequency of valve incompetence or absence.20 The internal and external jugular veins have a network of macrovenous interconnections, such as the venae comitantes communicating veins, and microvenous interconnections, such as the vasa vasorum. During retrograde flow drainage, these interconnections become pathways to accommodate venous blood and permit drainage to circumvent the valves.20,22 Furthermore, in the head and neck, the valve system is often less developed or in some cases absent, which allows for bidirectional flow.22
Retrograde-flow venous drainage through the distal superficial temporal vein is feasible because of the numerous venous interconnections in the head and neck and the high frequency of valve incompetence or valve absence.

The application of retrograde-flow venous drainage has also been applied to the internal and external jugular veins. In situations where distal branches of the external jugular vein were of inadequate caliber for anastomosis, case studies have demonstrated the feasibility of relying on its origin for anastomosis and retrograde flow. In other words, the external jugular vein can be ligated at the base of the neck, near its attachment to the subclavian vein, and transferred through a subcutaneous tunnel to reach the upper neck and face. Although this is a less desirable option since the vessel has likely been exposed to previous surgical manipulation and radiation effects, it may provide a “last-resort” type of solution for anastomosis in the vessel-depleted neck.

The internal mammary vessels are harvested at, or proximal to, the level of the third rib. This practice is employed because caudal to the third rib, the caliber of the vein diminishes significantly and often bifurcates. In 80% of patients, the vein bifurcates less than 2 mm distal to the fourth rib on the left side, and in 40% of patients on the right side. Most importantly, at the third rib, the artery averages 2.36 mm and the vein averages 3 mm in the majority of patients.

Given the possible history of, or future need for cardiac revascularization, the nature of the vein bifurcation, and the fact that the right internal mammary artery tends to be slightly larger, the right side is the preferred side for vessel harvest. The vessels can either be harvested with an incision over either the second, or more commonly, the third rib, to maximize pedicle length. Typically, a 3-cm horizontal skin incision is made over the rib, perpendicular to the axis of the sternum. The underlying pectoralis major can then either be dissected off the sternum and reflected laterally or can be split parallel to the direction of the muscle fibers to expose the underlying rib/costal cartilage. The most medial aspect, about 2 cm, of the costal cartilage is then removed, employing a subperichondrial dissection. Next, a small segment of the posterior perichondrium is incised and removed, exposing the underlying vascular bundle. The vessels can then be ligated and carefully dissected free from the underlying parietal pleura. Care must be taken during the dissection to avoid inadvertently puncturing the parietal pleura and creating a pneumothorax. The vessels can be freed.

The internal mammary vessels are harvested at, or proximal to, the level of the third rib because caudal to the third rib, the caliber of the vein diminishes significantly and often bifurcates.

**29.5 Internal Mammary Vessels**

In situations where the transverse cervical vessels are not available, the internal mammary vessels are an excellent choice for reconstruction of defects in the neck. Although less frequently used in head and neck reconstruction, the internal mammary vessels are a mainstay of breast reconstruction, demonstrating their feasibility and reliability.

The internal mammary artery originates from the subclavian artery, and the internal mammary vein drains into the brachiophalic vein. Together, these vessels can be found traveling along the undersurface of the upper six costal cartilages, approximately 1 to 3 cm lateral to the sternal margin. The internal mammary vessels are harvested at, or proximal to, the level of the third rib.
up and dissected subcostal about 3 to 4 cm superiorly toward their origins at the subclavian artery and brachiocephalic vein. At the inferior portion of each rib, the branching intercostal vessels must be ligated to allow for mobilization.26 With the internal mammary vessels free, they may then be “flipped up” and transposed into the low neck (▶ Fig. 29.6).2,24 If during the initial exposure, the medial aspect of the pectoralis major was dissected off the sternum, the divided pectoralis major muscle may be placed back into the defect generated by the rib removal to eliminate the dead space from harvest. If the pectoralis muscle was split, a drain should be placed.

Note
The right internal mammary artery tends to be slightly larger than the left side, so it is the preferred side for vessel harvest.

The internal mammary vessels are ideally suited for reconstruction of defects in the lower neck, and can be readily used for pharyngoesophageal reconstruction.2 In their final anastomosis, the vessels are transposed 180 degrees over the clavicle, with an anastomosis performed at the level of the clavicle or low neck.2

29.6.1 Thoracoacromial Artery
The thoracoacromial artery is a branch of the second portion of the axillary artery, originating from the segment located deep to the pectoralis minor.31 The artery courses medial to the pectoralis minor before penetrating through the clavipectoral fascia, which is the fascial layer between the pectoralis minor laterally and the subclavius muscle and clavicle superiorly.30,31 Once through the fascial layer, the thoracoacromial artery gives rise to four main named branches: the pectoral, deltoid, clavicular, and acromial arteries, each of which can potentially be used for microvascular anastomosis. Based on cadaveric studies, the arterial diameters average approximately 2 mm (deltoid artery 2.4 mm, pectoral artery 1.9 mm, acromial artery 1.4 mm, and clavicular artery 1.2 mm), and venous diameters average 2 to 3 mm.31 Most importantly, these branched arteries maintain their diameters for lengths of 4 to 5 cm, making them good candidates for microvascular reconstruction. Unfortunately, however, the named vein branches typically taper significantly in diameter with length. For this reason, the cephalic vein is often harvested for the venous anastomosis, given its more consistent and preferable dimensions.30,31
Several pedicled flaps can be based off the thoracoacromial system and its overlying cutaneous tissue; as such, care must be taken during dissection not to inadvertently eliminate those options for future salvage procedures. Specifically, the pectoralis major myocutaneous flap is based on the pectoralis branch of the thoracoacromial trunk, and the deltopectoral pedicle flap relies on the skin and subcutaneous tissue overlying the thoracoacromial vessels. Caution should be used when a nearby pedicle flap has previously been harvested, as the thoracoacromial/cephalic system may have been compromised. A thorough understanding of this vascular anatomy and its potential previous or future manipulation is important for successful dissection.

### Similar to the incision used to raise a deltopectoral flap

To access these vessels can be gained through a curved incision over the deltopectoral groove. The lateral aspect of the clavicle, the pectoralis major, and the deltoid are exposed. A horizontal incision is then carefully made through the pectoralis major, freeing its lateral clavicular attachments while maintaining the integrity of the underlying pectoralis minor. Dissection is then continued superolaterally in the plane between the pectoralis major and minor to identify the thoracoacromial trunk and its takeoff from the axillary artery. Generally, the artery is found piercing through the clavipectoral fascia about 6 to 10 cm lateral to the sternoclavicular joint, near the midclavicular line.

Once the thoracoacromial artery has been identified, the branches can then be dissected out distally as needed. Although there are several branches of the thoracoacromial trunk, typically only the deltoid and pectoralis branches are of sufficient caliber. Use of the pectoralis branch is generally avoided, given its potential for use as part of a pectoralis major rotational flap for salvage therapy.

It should be noted that the use of the thoracoacromial trunk for a previous flap is not a contraindication for using the thoracoacromial/cephalic system for anastomosis in the vessel-depleted neck. In fact, if the pectoralis major muscle has been rotated/flipped over the clavicle for a pectoralis major myocutaneous flap, the pectoral artery assumes a superficial orientation in the neck and becomes more easily accessible for anastomosis.

Prior to dissection, the pectoral artery can be palpated or a Doppler ultrasound may be used to trace back and locate the thoracoacromial trunk. In instances where the pectoralis major flap has been used, if sufficient time has passed for neovascularization, the pectoralis artery itself can be used for anastomosis without risk of compromise of the previous myocutaneous flap. Interestingly, the thoracoacromial system is unique in that two flaps can be harvested simultaneously—a free flap anastomosis can be performed with the thoracoacromial/cephalic system at the same time as the pectoralis myofascial flap, allowing for complex reconstructions and coverage of vital structures in the neck.

### 29.6.2 The Cephalic Vein

Since first described in 1992, the cephalic vein has become a “lifeboat” in the vessel-depleted neck. Prior to its popularization, many surgeons often relied on vein grafts or size-mismatched vessels for the Anastomosis, which predisposed patients to higher rates of flap failure. However, the cephalic vein has eliminated several of these risks by requiring only one anastomosis, offering ample length to reach defects throughout the head and neck, and providing a large-caliber vessel from outside the radiation field.

The cephalic vein maintains an anatomically predictable course, and because of its superficial nature can often be visualized preoperatively, facilitating dissection. The cephalic vein begins on the lateral aspect of the wrist and courses up the ventral forearm to the antecubital fossa. There, the cephalic vein communicates with the deep venous system via perforators and the basilic vein via the median cubital vein. The cephalic vein then ascends through the lateral bicipital groove between the biceps brachii and brachioradialis to reach the deltopectoral groove (Fig. 29.7). In the deltopectoral groove, the vein courses superficially to the medial aspect of the pectoralis minor (just inferior to the clavicle), where it then pierces the brachial fascia and travels with the deltoid branch of the thoracoacromial artery to the axillary vein.

As described previously, access to the cephalic vein is gained by creating a curved incision over the deltopectoral groove, taking care to consider preserving a potential deltopectoral flap skin paddle for future use. The clavicular head and lateral attachment of the pectoralis major are then exposed. The vein is then found coursing within the deltopectoral groove, between the deltoid muscle and pectoralis major. Once located, the vein can then be exposed distally with one linear incision, or for a more cosmetic harvest, dissection can be carried out through serial, fine incisions. Once adequate length has been dissected, the vein is ligated distally and transposed into the neck, face, or scalp. To facilitate this transposition, the vein is dissected proximally toward its attachment at the axillary or subclavian vein. Dissection ceases at the location where the cephalic vein penetrates the clavipectoral fascia, which serves as the anchor point for the transposition of the vein over the clavicle and into the head and neck (Fig. 29.8). To prevent torsion and kinking upon transposition of the vein, it is recommended that a cuff of adipofascial tissue remain attached around the vessel during dissection.

The cephalic vein has an attractive large caliber, and furthermore, the cephalic–subclavian venous system is considered a “high-flow low-pressure” system, which provides adequate venous drainage for bulky flaps and flaps with high metabolic demand in the head and neck. Depending on the location of the defect, the entire cephalic vein to the level of the wrist can be harvested, though it is generally preferred to ligate proximal...
to the antecubital fossa. Postoperatively, because of the superficial course of the vein, the venous outflow can be easily monitored via Doppler, which is especially helpful for buried flaps.\(^6\)

### Note

To prevent torsion and kinking upon transposition of the vein, it is recommended that a cuff of adipofascial tissue remain attached around the vessel during dissection.

The radial forearm flap is in a unique anatomical position given its reliance on the cephalic vein for its venous drainage and its frequent use in head and neck reconstruction. The majority of flap failures in the vessel-depleted neck are related to venous thrombosis. To prevent this complication when using a radial forearm free flap, some microvascular surgeons have taken advantage of the anatomy of the cephalic vein to create a modified radial forearm flap called the “semi-free radial forearm flap.”\(^6\)

In this reconstruction option, the radial forearm flap is raised and the artery is ligated at the antecubital fossa, but the vein is dissected up to the deltopectoral groove, where it remains intact for venous drainage. In select cases of vessel-depleted necks, this flap may be a uniquely appropriate option; only an arterial anastomosis is required.

### 29.7 The Common and Internal Carotid Artery

Previously, the common carotid and internal carotid arteries had not been considered as an option for microvascular anastomosis in the head and neck. Traditionally, during anastomosis, the carotid system would need to be occluded for a significant
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Although in theory the PI system provides an excellent solution for arterial anastomosis, the technique is not free of potential complications. Atherosclerosis affects the carotid artery, and performing an end-to-side anastomosis through an intimal plaque can lead to turbulent flow at the anastomotic site, providing a nidus for thrombus formation. Also, the carotid artery is fixed in its location, and an end-to-side anastomosis is more prone to stretch, rupture, and kinking with postoperative movement when compared to the more common end-to-end anastomosis. Lastly, the size of the carotid arteriotomy greatly influences the rate of arterial inflow, and if the arteriotomy is too large, it can rapidly lead to vascular congestion of the free flap, a problem even more common in the vessel-depleted neck.

29.8 Imaging in the Vessel-Depleted Neck

In the irradiated and postsurgical neck, vascular anatomy can be ambiguous, making surgical planning more complicated. Therefore, head and neck surgeons must rely on a combination of clinical, radiologic, and intraoperative findings to determine the most appropriate vessel selection. Fortunately, modern technology has enhanced our ability to detect vascular abnormalities preoperatively.

At the present time, there is no consensus about the best preoperative method for evaluating vascular anatomy. Traditional angiography, or digital subtraction angiography (DSA) (∈ Fig. 29.10a) had long been considered the gold standard but use of computed tomography angiography (CTA) (∈ Fig. 29.10b) has now become commonplace. Further, there are opportunities and situations in which modalities such as magnetic resonance angiography (MRA) and color duplex angiography provide good alternative options. DSA’s utility is limited by its invasiveness and potential complications, owing largely to requirement of transfemoral catheterization. Severe complications, such as transection or dissection of vessels, and embolization of detached plaques or thrombotic material leading to neurologic complications, are seen in 1.3 to 4.5% of cases.

Most recently, within the past 5 to 10 years, focus has turned to CTA for preoperative planning. Studies have demonstrated its noninferiority to DSA, with CTA demonstrating a sensitivity of 94% and specificity of 97% for detecting vascular abnormalities. While providing equivalent preoperative information, CTA is less invasive, involves less radiation exposure, is quicker and cost-effective, and perhaps most importantly, provides more anatomical detail than DSA. In addition to providing information about the vascular anatomy, CTA provides three-dimensional image rendering options, allowing the surgeon to see the vasculature in relation to the surrounding soft tissues. CTA has the additional ability to add and subtract bone, soft tissue, arteries, veins, and hardware, thereby providing superior spatial details. A recent report by Chen et al reported their use of CTA in preoperative surgical planning in the postoperative, irradiated neck. They were able to effectively classify their patients’ CTA findings into three groups: (1) patent recipient arteries, (2) presence of vessels but evidence of stenosis or atherosclerosis, and (3) no patent recipient vessels in the neck bilaterally. Of the patients in group 2,
half were determined to have vessels of adequate diameter for microvascular anastomosis; all others required use of pedicle flaps for reconstruction. In their experience, when compared to their intraoperative findings, CTA proved a reliable and recommended method for preoperative planning. However, CTA is not without limitations. CTA is susceptible to artifacts created by metallic hardware, which can make the images difficult to read and interpret. Additionally, CTA requires a contrast load, which, like DSA, limits its use in patients with renal impairment.

Two other imaging modalities that have more limited use in head and neck reconstruction are MRA and color-coded duplex ultrasound. MRA is advantageous in its lack of ionizing radiation; however, it tends to overestimate the severity of vessel stenosis it provides inferior spatial resolution and cannot detect intravascular calcification or combine information about bones and vessels in the same three-dimensional reconstruction. Color-coded duplex ultrasound is inexpensive, readily available, and can provide dynamic information about blood flow. Although this modality is widely used in preoperative evaluation for carotid endarterectomy, it is less suitable for evaluation of the branches of the external carotid artery. Furthermore, the evaluation is highly operator dependent, which is all the more complicated in the postoperative, irradiated neck. However, if visualized, color-coded duplex has a sensitivity of 86 to 94% for near occlusion and 100% for total occlusion of vessels.

Reconstruction of defects in the postoperative, irradiated neck can be exceptionally difficult, and preoperative planning, including an understanding of the current state of the vasculature, is crucial to the success of a reconstruction.

29.9 Conclusion

With improving survival outcomes, it is not uncommon for the head and neck surgeons to encounter patients who have undergone several prior treatments leaving their neck devoid of the commonly used vessels for microvascular anastomosis. These patients provide a unique challenge to the microvascular surgeon. To successfully overcome the challenge, the surgeon must have adequate knowledge and understanding of the various alternative options available. Options outside the previous treatment field include the transverse cervical vessels, the superficial temporal vessels, the internal mammary vessels, the thoracoacromial/cephalic system, and direct anastomosis to the common carotid or internal carotid. Modern imaging techniques may be used to help elucidate vascular anatomy in the complex, previously treated, vessel-depleted neck. The success of the reconstruction perhaps relies most importantly on the surgeon’s understanding of the various options available and ability to tailor his or her surgical approach based on each patient’s individual anatomy. Although posing a challenge, even in the vessel-depleted neck, rates of successful microvascular free tissue transfer should not be compromised.

References

The Vessel-Depleted Neck: Microvascular Reconstruction


Salvage Surgery: Minimizing Wound Complications

30 Salvage Surgery: Minimizing Wound Complications
Daniel I. Kwon and Eric M. Genden

30.1 Introduction
The treatment of recurrent head and neck cancer remains a difficult clinical problem for head and neck surgeons. In the era of radiotherapy, salvage surgery and its associated challenges have risen over the past several decades. In addition to recurrent cancer, non-oncologic ablative surgery is often required for late radiation sequelae such as osteoradionecrosis or non-functional larynx. Surgery occurring in a previously treated tissue field is suboptimal from several different aspects. Previously irradiated tissue has been well demonstrated to have impaired vascularity and altered biochemical cell function. Additionally, other factors such as malnutrition, low performance status, and poor general medical condition are nearly ubiquitous in this patient population. These factors coupled with the anatomy of the upper aerodigestive tract often lead to fistula, abnormal scarring, chronic infection, and other wound complications after salvage surgery. Microvascular free tissue transfer has become the standard treatment for defects in head and neck salvage surgery with reported success rates of greater than 90% in most series, even in the setting of previous irradiation or surgery in individual reports. Nevertheless, healing and reconstruction outcomes are worse in salvage cases with a high prevalence of wound healing complications. Reconstruction of nonhealing wounds and salvage surgery defects remain a challenge to surgeons and patients. A comprehensive approach considering the patient’s medical and surgical risk factors along with an understanding of the biological and clinical basis for impaired healing is important to combat this unfavorable scenario.

Note
The rate of fistula, abnormal scarring, chronic infection, and other wound complications after salvage surgery is approximately 50%.

30.1.1 Wound Biology and Pathophysiology
The physiology of wound healing has been well studied and is often described as broadly divided into phases of hemostasis, inflammation, proliferation, and remodeling. Wound healing is typically well orchestrated involving the interplay of multiple cell types, cytokines, and growth factors that work to regulate one another. Abnormal healing and chronic wounds arise from disruption of these processes. There are multiple local and systemic factors that contribute to poor wound healing (Table 30.1). Salvage surgery in the setting of head and neck cancer invariably involves several of these factors including general performance measures such as Karnofsky Performance Score and ECOG Performance Status that have been independently associated with wound complications in head and neck surgery.

Recurrent oncologic neck surgery is required in a significant subset of patients due to locoregional recurrence or second primary. These patients often require two or three surgeries as well as chemoradiotherapy to achieve locoregional control. Previously operated fields exhibit distorted tissue planes and fascial compartments that are replaced with scarring (Fig. 30.1). Additionally, disruptions of normal vascular and lymphatic pathways lead to hypoperfused tissue, higher tension, and susceptibility to poor healing. Previous neck dissection has been associated with increased wound infections, revision surgery, and free flap failure. Additionally, the majority of head and neck cancer involves the upper digestive tract, which introduces micro-organisms to healing wounds potentially leading to infection, fistula formation, or other healing complications. Perhaps most importantly for the operating surgeon, vessel depletion and absence of landmarks can be problematic for additional surgery and reconstructive efforts. The previously operated neck greatly increases the technical difficulty of surgery and consequently increases operative time, increases surgical complications, and often requires more complex reconstruction techniques.

Table 30.1 Factors that impede wound healing

<table>
<thead>
<tr>
<th>Factors that impede wound healing</th>
<th>Local</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood supply</td>
<td>Advanced age</td>
<td></td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Malnutrition</td>
<td></td>
</tr>
<tr>
<td>Microorganisms/infection</td>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Foreign body</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Nonviable tissue</td>
<td>Immunosuppression</td>
<td></td>
</tr>
<tr>
<td>Tension/mobility</td>
<td>Stress states</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Drugs/corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>Smoking and alcohol</td>
<td></td>
</tr>
<tr>
<td>Smoking and alcohol</td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Other systemic disease (connective tissue disorders, metabolic disorders, vasculopathies, etc.)</td>
<td></td>
</tr>
</tbody>
</table>
endothelial cells that are vacuolized. Similarly, the tunica media and adventitia show fibrosis, hyalinosis, and loss of smooth muscle cells and fibroblasts. Normal extracellular matrix is reduced and replaced by calcifications.9,10 These changes are initially acute but become chronic with abnormal collagen deposition without appropriate remodeling. Similar to blood vessel changes, surrounding connective tissue and lymphatic systems are affected as well.11 The resultant fibrotic tissue is chronically hypoxic and hypocellular. Blood vessels are sparse and diminished in diameter and less responsive to angiogenic or vasodilatory mediators.1 Ultimately, tissue treated with radiation and chemotherapy is poorly equipped to react to new injury and thus more prone to developing wound complications.

The specific role of chemotherapy to local tissue has not been well studied. Studies have drawn statistically significant associations with prior chemotherapy to wound complications.12 However, chemotherapy is most commonly associated with radiotherapy and it is difficult to delineate its specific impact. As a sensitizer, chemotherapy likely compounds the cellular effects of radiation leading to impaired healing. Additionally, chemotherapy may have a profound negative effect on the systemic medical condition of the patients. With the emerging role of neoadjuvant chemotherapy in head and neck cancer, further understanding of the tissue effects of chemotherapy is required.13

### Table 30.2 Wound healing complications

<table>
<thead>
<tr>
<th>Wound healing complications</th>
<th>Minor</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>Free flap failure</td>
<td></td>
</tr>
<tr>
<td>Seroma</td>
<td>Salivary fistula (requiring surgery)</td>
<td></td>
</tr>
<tr>
<td>Low-flow chyle leak</td>
<td>High-flow chyle leak</td>
<td></td>
</tr>
<tr>
<td>Skin edge necrosis/dehiscence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary fistula (amenable to wound care)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 30.1.2 Wound Complications in Salvage Surgery

Patients undergoing salvage surgery are at high risk for wound-related complications such as infection, bleeding, osteoradionecrosis, wound dehiscence, flap failure, and fistula (> Table 30.2). Wound complications may be delineated into minor versus major complications. Most studies define major wound complications by the need for prolonged hospitalization, reoperation, or life-threatening complications. Wound complication-related mortality is most common from sepsis or carotid blowout. Most of the literature on salvage head and neck surgery is found in laryngeal cancer. Following the paradigm shift toward organ preservation and primary chemoradiotherapy for the treatment of advanced laryngeal cancer, associated salvage total laryngectomy became more prevalent. These patients undergoing salvage laryngectomy were found to have major wound complications in approximately 60% of cases, reaching up to 80% in some series.14,15 Specifically examining pharyngocutaneous fistula rates reported incidences vary widely from specific studies ranging from 3 to 75%. However, pooled results show a significantly higher rate of fistula in salvage laryngectomy (~30%) versus primary laryngectomy (~10%).16,17 Furthermore, the effect of radiation on fistula rates has been found to be dose dependent with high-dose radiation being associated with significantly higher fistula formation.15,16 Finally, when present, fistula in the setting of previous radiation results in longer healing times and higher rates of reoperation.17

Note

Wound complication-related mortality is most common from sepsis or carotid blowout and the effect of radiation on fistula rates has been found to be dose dependent with high-dose radiation being associated with significantly higher fistula formation.

Rates for wound complications in salvage head and neck surgery have improved from previously reported rates due to increased experience by surgeons operating on irradiated tissue. Vascularized tissue reconstruction has been the mainstay of combating impaired wound healing in salvage surgery. Locoregional flaps that were recognized have conferred a reduction in wound breakdowns when compared to primary reconstruction early in the usage of radiotherapy.18,19 Microvascular free tissue transfer has expanded this principle greatly with an array of donor options and the ability to reconstruct...
ever more complex defects. With increased experience and refined techniques, microvascular free tissue transfer has been able to combat many of the healing difficulties that salvage surgery poses. Usage of free flap reconstruction in salvage laryngectomy has shown to confer a 43% decrease in risk of fistula formation in a recent meta-analysis. The pooled rate of pharyngocutaneous fistula has shown to be 31% in primary closure versus 22% with a vascularized flap in meta-analyses.20,21

**Note**
Free flap reconstruction is associated with a 43% decrease in risk of fistula formation following salvage laryngectomy.

Despite the clear advantages of using free transfer of nonirradiated tissue, poor healing in the salvage surgery is still a practical challenge. Many series have failed to show any difference in free flap outcomes and wound despite the well-known vascular changes and prothrombotic states that irradiated tissues pose complications between irradiated versus nonirradiated patients.22,23 Despite these encouraging statistics, most individual studies, even from high-volume centers, represent relatively small cohorts of heterogeneously treated patients. Additionally, many studies investigating free flap outcomes focus on free flap failure or anastomotic failure, a relatively rare event, as their primary outcome factors. Other wound complications such as partial necrosis, dehiscence, and salivary leak may be underreported or are inconsistently recorded. However, when systematically reviewed, previous radiation has been shown to have statistically worse free flap survival, secondary wound complications, and fistulas compared to nonirradiated patients on meta-analysis.24 These wound and flap complications, as with laryngectomy fistula rates, have been shown to be radiation dose dependent.25

### 30.1.3 Strategies for Management of Salvage Surgery Patients

**Preoperative**

Patients with head and neck cancer requiring salvage surgery invariably have multiple barriers to wound healing. A comprehensive approach is necessary to optimize outcomes and avoid complications. Preoperative planning with appropriate imaging, multidisciplinary discussion, ablative and reconstructive plans are important to select the appropriate intervention. Treatment should ideally be given at a high-volume tertiary care center with experienced inpatient care teams. The operating surgeon should have a clear plan preoperatively with expertise in a variety of free flaps as well as vessel harvest with backup reconstructive options. The patient should be well educated and have realistic expectations regarding postoperative course and the possibility of additional treatment, reoperation, and wound care.

**Note**
Preoperatively, the operating surgeon should have a clear plan and possess an expertise in a variety of free flaps as well as backup reconstructive options.

As discussed previously, there are many patient health risk factors for poor wound healing that have been associated with worse outcomes in head and neck cancer surgery and salvage surgery.2,26 Some predispositions to poor wound healing are innate, but certain factors such as nutrition, blood sugar control, smoking, and alcohol abuse can be optimized prior to surgery. Tobacco and alcohol cessation counseling should be provided. While nonsmokers have been shown to have improved healing outcomes after surgery when compared to smokers, even short-term perioperative tobacco cessation is associated with lower postoperative infection rates.27 Nutrition referral or encouragement of maximizing nutrition should be routine. In some patients, preoperative gastrostomy tube may be prudent. Finally, the consultation or communication with other medical providers is important to optimize the patient’s medical condition. Controlling blood sugar, managing immunosuppressant medications, optimizing thyroid levels, improving pulmonary function are all important factors for preoperative planning as well as for promoting healing postoperatively.

**Antibiotics**

Perioperative antibiotics should be given, especially considering head and neck surgery typically involves a clean-contaminated field. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been linked to postoperative infections and fistula in head and neck surgery.28 Studies have shown that a short perioperative antibiotic course is as effective as prolonged antibiotics in primary head and neck surgery in preventing surgical site infections, with prolonged courses being associated with additional risk.29 Studies looking specifically at free flap reconstruction have supported the evidence favoring short-term antibiotics versus long term.30,31 However, in salvage surgery, an optimal prophylactic antibiotic length is unclear. A recent study comparing 24-hour antibiotic prophylaxis with a prolonged course showed a high rate of postoperative infections in the short-term course but did not achieve statistical significance.32 Ultimately, salvage surgery encompasses a range of infection risk and antibiotics should be used judiciously by the clinician’s discretion when deviated from standard perioperative recommendations.

**Note**
Short perioperative antibiotic course is as effective as prolonged antibiotics in primary head and neck surgery in preventing surgical site infections, with prolonged courses being associated with additional risk.

General principles of optimal operative technique remain especially important in salvage surgery. Each surgical decision from...
Skin incision design to suture placement becomes more significant to the overall outcome. Poor skin incision planning or a high-tension closure may result in skin breakdown and exposure of underlying structures such as the carotid artery. Modifications of the MacFee or apron incision have been shown to largely avoid issues of skin flap necrosis that were problematic with other incisions used in the past.32,34 Plating and implant use should be used with caution due to high rates of extrusion and infection.35 These risks are especially high if hardware is placed under areas of thin soft tissue coverage, exposed to saliva, or is prone to biofilm formation.

**Local Wound Care**

The general principles of local wound healing involve decontamination, preventing further trauma, and optimizing the local environment. Chronic wounds often exhibit colonization of bacteria and bacterial count has been associated with delayed wound healing.36 In head and neck surgery, contamination with saliva or mucus is a frequent problem. Every effort to separate wounds from contamination should be done. In cases of large salivary contamination due to dehiscence or fistula, catheterization with T-tube or Malecot or surgical formalization may be used to divert saliva until delayed closure. Wounds should be thoroughly washed to reduce bacterial load. A variety of topical treatments and dressings have been described to decrease colonization including Dakin’s hypochlorite solution, topical antibiotics, and silver-based dressings.37-39 Qualitative wound cultures may be done to differentiate between inflammation and infection. Systemic antibiotics may be used in the presence of local infection but have not been shown to aid in local wound healing and should not be used in the absence of active infection.40

Several topical treatments to optimize the local tissue environment have been described. Topical therapies including hydrocolloids, alginates, and other foams and gels have shown to be helpful in promoting a moist environment that promotes healing and reduces pain.41 Occlusive dressings are often used in chronic wounds to similarly prevent desiccation but should be used with caution due to high rates of contamination in the head and neck. Several active topical agents such as bioflavonoids and growth factors are being studied that have shown to upregulate the cellular mechanisms for healing in vitro and in animal models.42-47 Similarly, mesenchymal stem cell injection into radiation-related wounds are being studied in various experimental models and show promise.48,49,50,51

Traditionally, wet-to-dry dressing changes have been used for debridement of nonviable tissue and are still frequently used by surgeons to promote granulation tissue.40 Negative pressure wound therapy (NPWT) and enzymatic topical treatments are modern alternatives to remove nonviable tissue and exudates. Studies have shown them to speed up granulation and reduce patient discomfort with more frequent dressing changes. While there is a lack of randomized controlled data to demonstrate a clear healing advantage over traditional wound care,40-51 NPWT has been shown to decrease hospitalization stay, speed wound closure, and decrease associated morbidity compared with traditional wound care. The benefits of NPWT are well studied and have been commonly used in other parts of the body for the past two decades. Its adoption in the treatment of head and neck wounds has been more recent but has been shown to be similarly safe and effective.52,53

**Hyperbaric Oxygen Treatment**

Hypoxia and hypoperfusion are some of the primary underlying etiologies of poor wound healing in salvage surgery. Hyperbaric oxygen (HBO) therapy increases tissue oxygen tension and has been shown to promote angiogenesis, collagen formation, has antimicrobial properties.54 HBO has been used for a variety of acute and chronic wounds including radiation-associated wounds and proven to be efficacious in randomized controlled trials.55,56,57,58 One of the most common applications in head and neck irradiated patients is for osteoradionecrosis (ORN) where it has been shown to be effective when local treatment has failed.59 HBO is primarily indicated as an adjunct to conservative wound care strategies and can work synergistically with local wound therapy to obviate the need for more aggressive treatment.60 Recently, its application alongside vascularized flaps to improve outcomes has been an area of interest with promising results in animal models but lacks clinical evidence.61

**Surgical Reconstruction**

It is well established that reconstruction in salvage surgery, whether primary after resection or secondary for the treatment of chronic wounds, should be done with a vascularized flap. A variety of pedicle and free flaps have been described for various defects of the head and neck. There are no randomized controlled studies to help determine flap selection in salvage surgery reconstruction. Instead, flap selection is largely dependent on the particular defect, functional and aesthetic goals, and surgeon experience.

Pedicle flaps have traditionally been the workhorse of head and neck reconstruction due to their reliability and technical simplicity. The deltopectoral and pectoralis major free flaps have been well tried for the past several decades and have proven effective in a variety of applications.20,62,63,64 Other regional flaps such as the submental island and supraclavicular flap have also been used. However, pedicle soft tissue flaps have limited utility for complex head and neck defects and the donor sites may be included in the previous radiation field. With increasingly widespread expertise in microvascular free tissue transfer, pedicle flaps should only be used in selected cases.

Free tissue transfer is the gold standard for salvage surgery reconstruction and its application continues to be refined. Their use has been well described even in cases of multiple courses of radiation or recipient vessel depletion.7,65 In general, donor tissue selection should be appropriate to the defect and goals of
reconstruction. However, additional considerations should be taken by the reconstructive surgeon in regard to vessel size, pedicle length, and vascularity of the tissue to help guide donor sites. The use of muscle coverage has been shown to promote wound healing with its high vascularity, conforming ability to close dead space, and expressions of growth factors. Reconstruction with free flaps with significant muscle bulk includes the rectus abdominus, serratus, latissimus, or vastus lateralis. These sites may be harvested as a composite flap with skin and bone or as free muscle and fascia (Fig. 30.2, Fig. 30.3).

Note
The use of muscle coverage has been shown to promote wound healing with its high vascularity, conforming ability to close dead space, and expressions of growth factors.

The gastro-omental free flap is uniquely ideal for repair of high-risk wounds and has enjoyed a resurgence of interest due to the widespread use of chemoradiation and salvage surgery. This is primarily due to the rich supply of fibroblasts and progenitor stem cells from the omentum as well as the advantage of a highly vascular pliable tissue layer. Used in the past primarily for pharyngeal mucosal repair, the protective qualities of the omentum were recognized when they were used to help protect the carotid arteries in the era of routine radical neck dissections (Fig. 30.4). However, its popularity decreased in favor of less morbid donor sites. Recent series have reaffirmed its benefit in salvage surgery involving pharyngeal defects. The omental tissue can be used to bolster pharyngeal closures, acting as a protective overlay. The fibroblast-rich omentum has the capability of walling off salivary leaks with fibrous adhesions that can form within 3 hours. Additionally, the mucus secretions of the distal gastric mucosa help combat xerostomia, improving swallowing outcomes. Finally, the rich vascularity of the omentum allows for skin grafting to cover cutaneous defects (Fig. 30.5).

Ultimately, the advantages of free tissue transfer in aiding wound healing and reconstruction after salvage surgery is contingent on appropriate donor-site selection and inset design. Special consideration should be given to prioritize factors that will improve healing. The association of increased free flap anastomotic failure with previously irradiated patients, as well as timing and dose dependence, should be considered in planning.
Salvage Surgery: Minimizing Wound Complications

Fig. 30.5 The omentum can be covered with a skin graft.

30.2 Conclusion

For a variety of reasons, major ablative surgery after previous radiotherapy or chemoradiotherapy is required in a significant population of head and neck cancer patients. Salvage surgery is often necessary as the last remaining curative treatment option or simply to alleviate the morbidity of uncontrollable recurrence but is associated with significant wound healing complications. This is due to a multitude of factors that create conditions averse to the normal wound healing mechanism. Wound healing problems in salvage surgery represent a heterogeneous population with multiple codependent factors. Thus, there is a paucity of data to clearly guide specific treatment planning. However, the mechanisms of wound healing, tissue changes after irradiation, and chronic wound care outcomes are fairly well described. By utilizing a comprehensive approach to patient optimization and surgical planning, the barriers to wound healing may be overcome with favorable outcomes.

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