Oral Cancer

Evaluation, Therapy, and Rehabilitation

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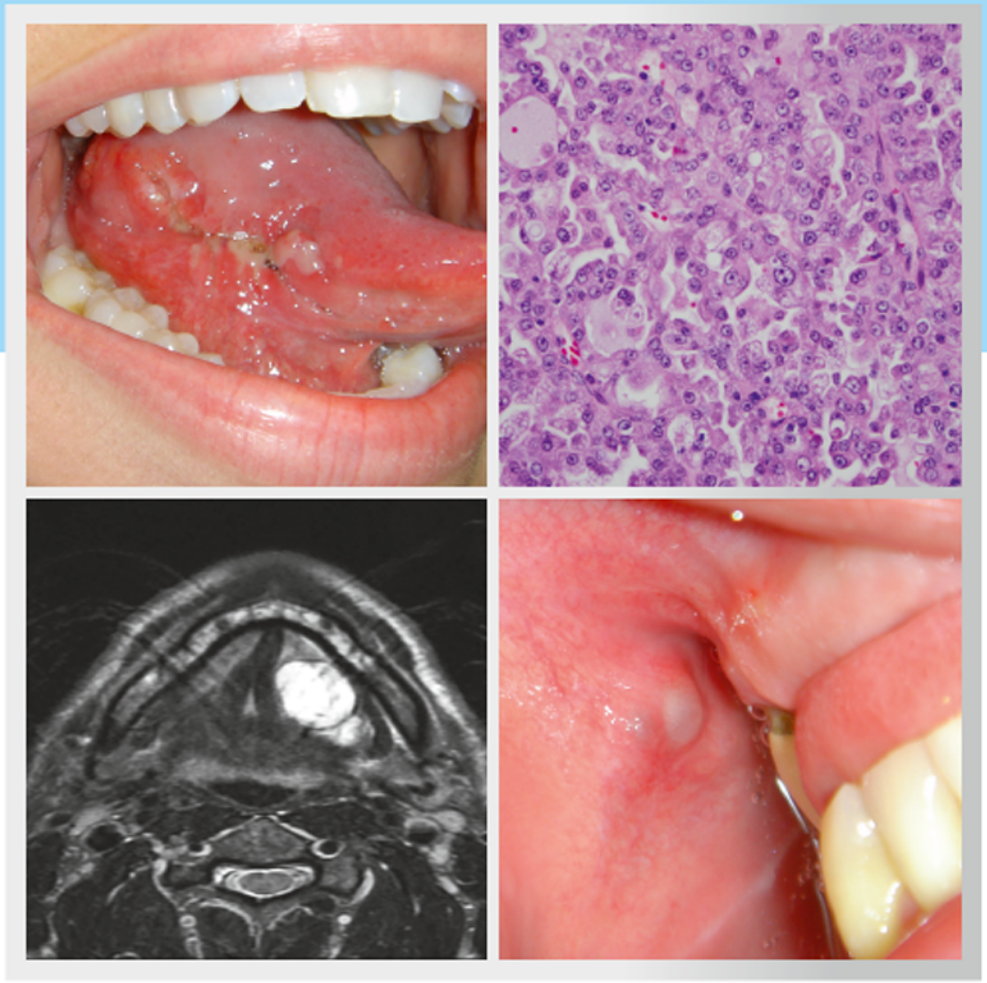

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Foreword

The management of squamous cell carcinoma of the upper aerodigestive tract has evolved significantly in recent decades. For patients with carcinoma of the oropharynx, hypopharynx or larynx, functional organ preservation through the application of new surgical and nonsurgical modalities has become the overarching principle of treatment, as the quest for therapies that provide significant survival benefit continues. In contrast, primary surgery remains the preferred treatment for patients with cancers of the oral cavity and has been demonstrated to provide better disease control and functional outcome than nonsurgical methods. Nearly 40 years ago, it was established that definitive radiation therapy for squamous cell carcinoma of the oral cavity was associated with an unacceptable incidence of severe fibrosis, xerostomia, and osteoradionecrosis of the jaws. Contemporary methods of reconstruction introduced in the late 1980s permitted transfer of vascularized soft tissue and bone to reconstruct the tongue, floor of the mouth, and mandible with a high degree of success and acceptable functional outcome. Reliable free tissue transfer now provides the head and neck oncologic surgeon with the latitude to resect tumors with adequate margins, knowing that advanced reconstruction would provide restoration of form and function and well-vascularized tissues that could better withstand postoperative radiotherapy. It is likely that the combination of more complete surgical resection, guided by contemporary imaging to assess the local extension of oral cavity tumors more accurately, and advanced reconstruction have contributed to the improved survival observed in these patients.

Oral Cancer: Evaluation, Therapy, and Rehabilitation is an important addition to the existing textbooks devoted to head and neck oncology. The editors are internationally recognized leaders with extensive experience in treating head and neck cancer. In this book, they have provided the most current evidence-based management principles available. Each chapter covering oncologic evaluation and treatment is paired with a companion chapter on state-of-the-art reconstruction particular to each site. A key element in the treatment of patients with oral cancer is contemporary surgical reconstruction, and leaders in the field have contributed site-specific chapters covering the reconstructive options that are time tested and effective for restoring form and function. The contributing authors stress the importance of multidisciplinary evaluation and management by a team of experts, which is a fundamental concept throughout this book.

The book starts with a discussion of epidemiology and the molecular events that are precursors to invasive cancer, providing an understanding of the molecular biology of oral cancer progression that is critical to developing risk assessment models and identifying targets for new therapies. On this broad foundation, subsequent chapters provide an in-depth discussion of patterns of disease progression and a comprehensive management approach for each of the oral cavity subsites. Appropriately, prosthetic rehabilitation, implantology, and speech and swallowing rehabilitation are covered in detail and serve as an adjunct to the chapters on therapy and surgical reconstruction. The textbook appropriately concludes with a discussion on the management of early and late treatment sequelae and strategies to mitigate these untoward events. These are followed by discussions on the future directions in cancer therapy that are unfolding and include the hope for immunotherapy and targeted therapy to improve treatment outcomes and lower morbidity. The scientific basis for these new modalities is addressed as well. This textbook is an important state-of-the-art resource for those who seek to become educated in managing patients with tumors of the oral cavity. Its comprehensive scope will be an invaluable resource for the multidisciplinary team whose responsibility is to comprehensively care for these patients with common goals of achieving a cure and providing a meaningful quality of life.

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Preface

Oral cancer comprises a significant proportion of head and neck malignant neoplasms worldwide and carries the potential to considerably disrupt form and function. Surgery, the primary treatment modality, can impair appearance, speech, mastication and swallowing, each of which may be further exacerbated by adjuvant treatments. Successful prevention and early detection of oral cancer remain elusive to date, yet it can be the best opportunity to reduce the suffering and mortality from oral cancer. Recent advances in the understanding of the underpinnings of oral cancer at the molecular level and in the immunological interface between tumor and patient have enabled progress towards more effective treatment strategies, which may also inform future prevention or early detection.

This textbook provides a comprehensive in-depth review of each phase of the survivorship trajectory for oral cancer patients. Oral cancer is a heterogeneous entity that can arise from divergent exposures and premalignant entities. At the diagnostic stage, the biopsy that is initially performed by a head and neck specialist is interpreted by a pathologist. While much of the diagnostic and therapeutic pathway hinges upon accurate pathologic evaluation, it also relies upon further assessment by neuroradiology, speech-language pathology, radiation oncology, medical oncology, nutrition, dentistry, psychology, social work, and nursing. The input of the multidisciplinary team is synthesized at each stage of care and this theme is carried through all stages of the survivorship trajectory.

In this book, the issues relevant to oral cancer in each phase are examined in-depth. For example, dental issues are examined separately from the vantage point of pre-treatment, postsurgical rehabilitation, postradiotherapy, dental complications of oral cancer treatment, and sequelae such as trismus. Swallowing and speech assessments before and after therapy are considered separately and include video illustrations. Strategies for radiation therapy as primary, adjuvant, and salvage therapy are explored as well as the sequelae and complications of radiation therapy. Given that surgery serves as the main treatment modality for the majority of histopathologic entities of oral cancer, surgical considerations for each subsite of the oral cavity are considered, not only from an ablative but also from a reconstructive perspective. For each chapter, epidemiology, typical clinical presentations, diagnostic methods, anatomic and treatment considerations, and sequelae of therapy are reviewed. With each chapter key considerations or pearls are highlighted. Lastly, recurrent and metastatic oral cancer management is discussed in a similar focused manner.

This book provides the present state-of-the-art diagnostic, therapeutic, and rehabilitative strategies for oral cancers with a consistent emphasis on the theme of multidisciplinary care. Due to the complexity of management of patients with oral cancer, their care must be carefully coordinated to allow access to a comprehensive team of experts who work collaboratively to ensure optimal treatment outcomes.

We are grateful to the experts who have contributed their insights, perspectives, and expertise to the content of this book. We hope that this book will assist practitioners at all levels of experience. We are optimistic that the future holds with it many advances and improvements in oral cancer care and outcomes.

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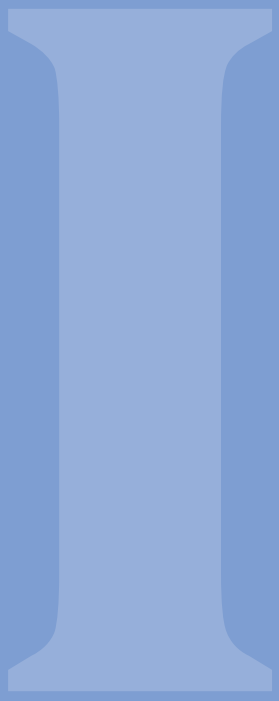
Section I

Background



1 Epidemiology of Oral Cavity Cancer

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Summary
Oral cavity cancer is one of the most common cancers worldwide. The leading risk factors include the use of tobacco, alcohol, and betel quid, which is predominantly used in Asia. Fortunately, the overall incidence and survival in the United States have improved with the decrease in tobacco use. Recommended treatment generally includes definitive surgery, with adjuvant therapy in indicated cases. The most important prognostic factor is the presence of nodal metastasis, and overall survival decreases dramatically as overall stage increases. Therefore, early detection of premalignant or malignant lesions could lead to improved survival. Resection and reconstruction of oral cavity malignancies are uniquely challenging, as they require consideration of both structure and function and can lead to significant posttreatment changes in quality of life. This chapter will provide an overview of the epidemiology, risk factors, clinical presentation, anatomy, and treatment considerations of this complex disease.

Keywords: epidemiology, risk factor, clinical presentation, anatomy, treatment

1.1 Introduction

Oral cavity cancer is among the most common cancers worldwide and is often associated with significant patient morbidity and poor survival. Patients may have advanced disease at presentation and therefore require treatment with surgery, radiation therapy, and chemotherapy. While surgical advances over the last 40 years have resulted in better functional outcomes, oncologic outcomes for oral cavity cancer are largely unchanged.[1] Over the last several decades, there has been an increased understanding of etiologic factors associated with oral cancer that extends beyond traditional carcinogenic factors. Investigators have focused on the impact of diet and dental health as potential etiologic factors and have explored the increasing incidence of oral cavity cancer among younger patients. In this chapter, we review the epidemiology of oral cavity cancer, with an emphasis on highlighting established and emerging risk factors associated with this disease. A complete understanding of oral cancer epidemiology is essential towards targeting interventions and improving primary and secondary prevention for oral cavity cancer.

1.2 Epidemiology

1.2.1 Histology

Squamous cell carcinomas constitute more than 90% of all oral cavity cancer and will be the focus of this chapter. However, other malignant tumors can arise from the epithelium, connective tissue, minor salivary glands, lymphoid tissue, and melanocytes. Minor salivary gland carcinomas represent less than 5% of the oral cavity cancers. Most arise in the hard palate (60%), lips (25%), and buccal mucosa (15%). Mucoepidermoid carcinoma is the most common type (54%), followed by low-grade adenocarcinoma (17%), and adenoid cystic carcinoma (15%). Other tumors are mucosal melanomas, osteosarcoma of the mandible or maxilla, and odontogenic tumors such as ameloblastoma.[2]

1.2.2 Incidence/Burden of Disease

Oral cavity squamous cell carcinoma (OCSCC) is one of the most common head and neck cancers, accounting for approximately 30% of all cases. In the United States, from 2000 to 2010, the incidence of oral cavity cancer was 4.3 per 100,000. Globally, the age-standardized rate was 2.7 per 100,000 with substantial differences by region, race, and sex. In general, rates of oral cavity cancer are higher in southern Asian counties with Papua New Guinea, Maldives, Sri Lanka, and Pakistan with the highest rates.[3]

Race and Gender Distribution

In the United States, from 2000 to 2010, the incidence of OCSCC was much higher among non-Hispanic white males (6.4 per 100,000 population, age-standardized to the 2000 population) compared to non-Hispanic black males (4.2 per 100,000 population). This racial difference is also reflected in females (3.4 per 100,000 population), where non-Hispanic white women have higher rates than non-Hispanic black women (2.1 per 100,000 population). Hispanic males (3.4 per 100,000) also have higher rates compared to Hispanic women (2.1 per 100,000 population).[4]

Even globally, the incidence of oral cavity is consistently greater among men than among women. The male:female rate is 2:1 overall, and it is the highest for central and eastern Europe (5:2) and lowest for northern Africa, western Asia, and Oceania (1:4).[3]

Recently, there has been a dramatic increase in the incidence of oral tongue squamous cell carcinoma of young females, and to a lesser extent young males.[5,6] Studies of the prognosis of this subgroup are mixed with no clear consensus.[7–9] The genomic profile of older smokers with tongue cancer is shown to be the same as younger nonsmokers.[10] This subgroup was determined with epidemiologic methods, and since these tumors are not human papillomavirus (HPV) associated or smoking and alcohol related, the etiology remains uncertain.[11]

1.2.3 Survival

Survival for OCSCC has improved over the past decade.[4] In the Surveillance, Epidemiology, and End Results (SEER) Program, the 5-year overall survival is 57.1%.[12] There are some differences by race, with non-Hispanic blacks having the lowest 5-year survival at 42.7%, and non-Hispanic whites with a 58.0% 5-year survival. However, there is tremendous heterogeneity by stage. As stage increases, 5-year survival decreases dramatically. Five-year survival by stage I is 78.1%, stage II is 60.3%, stage III is 48.7%, stage IVA is 33.2%, stage IVB is 23.8%; and stage IVC is 12.3%.[12]

1.2.4 Risk Factors

Tobacco

Tobacco is the leading risk factor for OCSCC, accounting for over a quarter of OCSCC cases.[13,14] However, the association between OCSCC and tobacco is smaller than when compared to other subsites of head and neck cancer.[15–17] Previous epidemiologic studies have demonstrated that cigarette smokers have almost three times the risk of OCSCC when compared with noncigarette smokers.[18] Even low-frequency smokers (one to two cigarettes a day) have a 50% increased risk of OCSCC.[19]

Duration of smoking also plays an important role in OCSCC. A study found that at a low level of consumption (≤ 15 cigarettes per day), smoking more cigarettes per day for a shorter duration was more deleterious than smoking fewer cigarettes per day for a longer duration.[20] However, this relationship changes for heavier smokers (> 15 cigarettes per day). Among heavy smokers, smoking more cigarettes per day for a shorter duration was less deleterious than fewer cigarettes per day for a longer duration. The excess risk of OCSCC due to tobacco virtually disappears 20 years after smoking cessation and independently of the quantity previously consumed.[20]

Studies evaluating smokeless tobacco and OCSCC have been inconsistent. The relationship is complex due to the concurrent use of cigarettes or other fillers such as betel leaves, areca nuts, quicklime, condiments, spices, or sweeteners depending on the region. Animal models of smokeless tobacco have been largely negative. However, in the United States, smokeless tobacco (non-cigarette-smoking) users have demonstrated an approximately twofold increase in the risk of OCSCC.[21] Ultimately, the International Agency for Research on Cancer has concluded that there is sufficient evidence of carcinogenicity in smokeless tobacco.[22]

Alcohol Use

Although not as strongly correlated as tobacco use, high alcohol consumption is also a major risk factor for OCSCC. Alcohol accounts for an 18% increased risk of OCSCC.[15] The risk increases with daily consumption, duration of consumption, and lifetime cumulative consumption.[23,24] Heavy beer and liquor drinkers (30 + drinks per week) were about five times more likely than nondrinkers to develop OCSCC.[25] Heavy wine drinking was associated with an increased risk of OCSCC (odds ratio [OR] = 3.2), but there was an attenuated association most likely attributed to differences in socioeconomic status.[25]

Interaction between Tobacco and Alcohol Use

Smoking and alcohol consumption have a synergistic interaction that results in an exponentially increased risk in OCSCC and other head and neck cancers. Among never drinkers, heavy smokers had almost 13 times the risk of OCSCC compared with never smokers/never drinkers. However, among those who consume over two alcoholic beverages a day, heavy smokers had almost 31 times the risk of OCSCC compared with never smokers.[26] This same study suggests that 23.5% of OCSCC are attributed to both alcohol and cigarette smoking.[26,27]

Betel Quid

Betel quid contains betel leaf, areca nut, and slaked lime, and it may contain tobacco. It is used by 600 million people worldwide, predominantly in Asia.[28] Betel quid has been classified as an oral carcinogen in humans by the International Agency for Research on Cancer, with evidence for a dose–response relationship (i.e., risk increases in a step-wise fashion with increased exposure).[28] In Asian studies, betel quid chewing appeared to be a stronger risk factor for cancer than either smoking or alcohol consumption.[29] In a recent review, betel quid without tobacco was associated with a sevenfold increase in the risk of OCSCC and a 15-fold increased risk when betel was combined with tobacco.[30]

Diet

The most consistent finding between diet and OCSCC risk is the association between consumption of fruit and vegetables with decreased risk.[31] In a large prospective cohort study, high consumption of fruits and vegetables was associated with a decreased risk of OCSCC (OR = 0.6; 95% confidence interval [CI]: 0.4–0.9) when compared with low consumption of fruit and vegetables.[31] Since fruits and vegetables do not have a high source of protein or fat, carbohydrates, fiber, and vitamins and minerals likely contribute to this association. Other types of food have been studied less frequently and with inconsistent results. In a meta-analysis, high consumption of processed meat (i.e., meat preserved by smoking, curing, salting, or by addition of chemical preservatives) was associated with an increased risk (OR = 1.91; 95% CI: 1.19–3.06) of OCSCC. However, total meat (white and red meat) consumption was not significantly associated with OCSCC.[32]

To further strengthen the association between diet and OCSCC, studies have suggested a link between combined dietary indexes and OCSCC. In a case-control study, OCSCC was associated with a "western" diet, or a diet with high consumption of fried foods, fat, and processed meats.[33] In the same study, more pro-inflammatory diets were also associated with an increased risk.[34]

The association between tea and OCSCC is inconsistent and depends largely on the temperature of tea and location. Maté—an herbal tea commonly consumed in South America—was associated with an increased risk of oral cavity (and oropharynx) cancer.[35,36] Yet, a meta-analysis found a decreased risk of OCSCC with overall tea consumption. When the meta-analysis considered type of tea, green tea was significantly associated with decreased risk of OCSCC, while black tea was not associated. However, most of the green tea studies were in Asian countries, making them less generalizable.[37]

Similarly, coffee consumption is likely also associated with a decreased risk of OCSCC. A pooled analysis found an inverse relationship between OCSCC and coffee consumption (OR: 0.5; 95% CI: 0.3–0.7 for coffee drinkers of more than four cups of coffee per day vs. nondrinkers).[38] This association was also reflected in a French case-control study.[39] In a meta-analysis, coffee was associated with a decreased risk of OCSCC and pharyngeal cancer.[40]

Oral Human Papillomavirus Infection

Although HPV infection has been linked definitively to oropharyngeal cancer, its role in OCSCC etiology is controversial. In a

meta-analysis that included 5,478 cases worldwide, HPV deoxyribonucleic acid (DNA) was found in 24.5%.[41] Another study of 1,264 cases found 7.4% of OCSCC tumors had HPV DNA.[42] Both studies demonstrate large heterogeneity by region and sex, potentially leading to the difference in prevalence. To date, there is no clear molecular evidence that OCSCC is driven by HPV infection. Unlike oropharyngeal cancer, there does not appear to be a survival advantage for HPV-positive OCSCC.[43–47] Additionally, for OCSCC as a whole, no significant relationship was observed between high-risk sexual behaviors and the risk of cancer.[48]

Oral Health

Various measures of oral health, such as the number of missing teeth, number of dental checkups, and tooth mobility, have been associated with OCSCC.[49–52] Although these results could be confounded by low socioeconomic status and education level as well as the consumption of tobacco and alcohol, poor oral and dental health is a significant risk factor for OCSCC. In a pooled analysis, having the worst oral hygiene score was associated with three times greater risk of OCSCC when compared to having an optimal oral hygiene score.[50]

1.3 Clinical Presentation

Patients with oral cavity lesions (benign, premalignant, or malignant) often present initially to a primary care provider or dentist. Due to the wide variety of presentations and pathology in oral cavity lesions, they are often ambiguous and referred to an otolaryngologist or head and neck surgeon in order to rule out malignancy.

1.3.1 Benign Lesions

There are a variety of anatomic variants occurring in the oral cavity that can be confused with pathologic findings, including dental tori, Fordyce granules, and geographic tongue. Dental tori are bony outgrowths most commonly arising from the lingual surface of the mandible or the hard palate. They can be caused or exacerbated by trauma and generally do not require removal. Fordyce granules are small, papular sebaceous glands found in clusters, usually on labial or buccal mucosa. Again, these lesions are safe to leave alone. Geographic tongue, or benign migratory glossitis, presents with erythematous patches that migrate over the surface of the tongue. It is present in 3% of Americans and can often be confused with more concerning lesions such as leukoplakia.[53] Another lesion that sometimes causes concern among primary care providers or dentists is the iatrogenic dental amalgam tattoo. These lesions are found in approximately 1% of the U.S. adult population and can be mistaken for a nonbenign lesion. An amalgam tattoo presents most commonly as a dark-colored macule on mucosa adjacent to a restored tooth.[54]

Multiple categories of systemic illness can present with oral manifestations, including immunologic disorders (e.g., lupus, scleroderma, inflammatory bowel disease, human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS]), vitamin deficiencies (e.g., vitamin B12 deficiency), colonization or infection (e.g., candidiasis, herpes simplex virus), hematologic disorders (e.g., hereditary hemorrhagic telangiectasia), and endocrinopathies (e.g., hypothyroidism).

1.3.2 Premalignant Lesions

Premalignant oral cavity lesions can resemble benign lesions, but differ in that they have a risk of malignant transformation. Recognition and early detection are important in the prevention of OCSCC. Risk factors of both premalignant and malignant lesion development are similar and are discussed in the "epidemiology" section of this chapter. The most common premalignant oral cavity lesions are leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus.[55] Leukoplakia is a painless, white plaque determined by diagnosis of exclusion. Histologically, these lesions are comprised of hyperkeratosis with alteration in epithelial thickness. The risk of malignant transformation associated with leukoplakia is as high as 18% within 5 years.[56] Erythroplakia is overall less common, but it has a greater than 90% chance of transforming into a dysplastic or malignant lesion.[57] It presents as a red, flat macule with a velvety appearance. Oral submucous fibrosis is primarily found in southeast Asian countries where chewing betel quid is more common. It appears as a fibrotic, blanching oral mucosal lesion that can later lead to significant trismus. The risk of malignant transformation is 7.6% within 10 years.[58] Oral lichen planus (OLP) is characterized by inflammation of the stratified squamous epithelium, possibly from autoimmune activation of CD8+T cells. There are six types of OLP, the most common of which is the reticular pattern. This subtype presents as asymptomatic, often bilateral, and symmetric "fine white striae."[55] A 2010 review reported a risk of malignant transformation of up to 10%.[59]

1.3.3 Malignant Lesions

Malignant oral cavity lesions can be variable in appearance, presenting signs and symptoms, and location. Nonhealing ulcers, mucosal irregularities, and exophytic masses are common presentations of oral cavity malignancies (▶ Fig. 1.1, ▶ Fig. 1.2, ▶ Fig. 1.3). A complete history and physical examination is essential, with a focus on assessing risk factors and a complete head and neck examination. Symptoms can range from severe pain to hypoesthesia or anesthesia due to adjacent sensory nerve invasion. Trismus and bleeding are signs potentially concerning for malignant pterygoid invasion and tumor necrosis, respectively. A firm neck mass in a patient with an oral cavity lesion should increase suspicion for malignancy.

1.4 Diagnosis and Evaluation

1.4.1 Physical Examination

The first step on initial presentation is a comprehensive history and physical examination. A physical examination of the oral cavity should include visualization and palpation of all oral cavity subsites (oral tongue, floor or mouth, alveolar ridge, hard palate, buccal mucosa, retromolar trigone). The dentition should be evaluated, and dentures should be removed for better visualization. A full cranial nerve examination is a necessary component, with emphasis on tongue mobility (cranial nerve

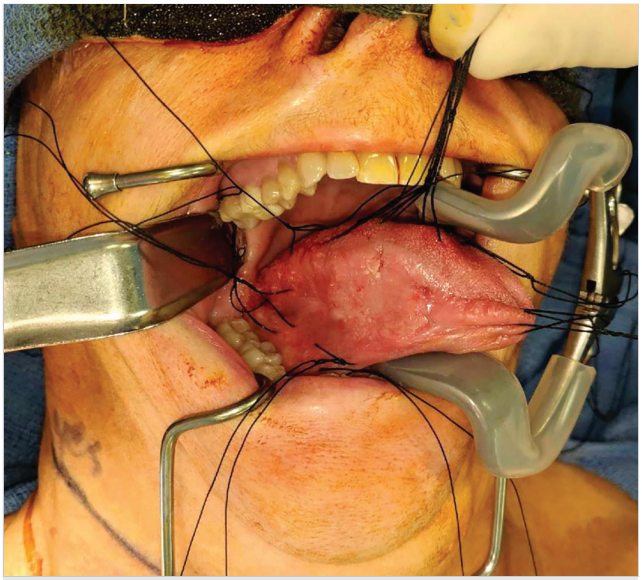

Fig. 1.1 Lateral tongue squamous cell carcinoma.

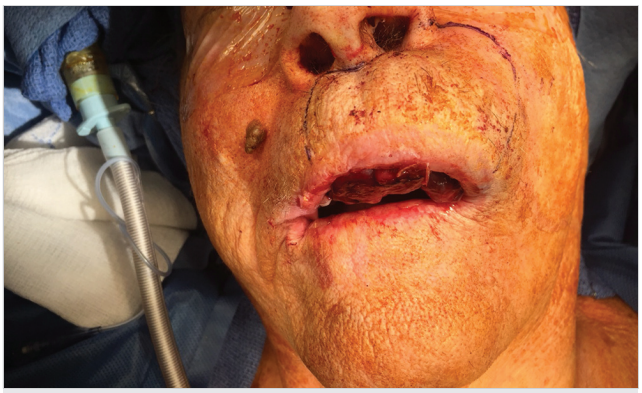

Fig. 1.2 Alveolar ridge squamous cell carcinoma.

XII) and sensation in the distribution of the inferior alveolar and mental nerves (cranial nerve V). The complete examination should also include either an indirect mirror or a direct fiberoptic view of the oropharynx and larynx. Understanding the extent or invasiveness of the tumor is essential when planning therapy, and clinicians should assess the potential for invasion into the deep muscles of the tongue, floor or mouth, mandibular or maxillary bone, or pterygoid musculature.

Imaging

Imaging is a critical tool in assessing tumor invasion of soft tissue and muscle, bone, or neural structures, as well as to evaluate for regional or distant metastases. The National Comprehensive Cancer Network (NCCN) recommends a computed tomography (CT) scan and/or a magnetic resonance imaging (MRI) with chest imaging as indicated and to consider a positron emission tomography (PET/CT) for advanced-stage disease. A CT scan with contrast is generally the mode of imaging performed during initial evaluation. It is very useful in assessing tumor

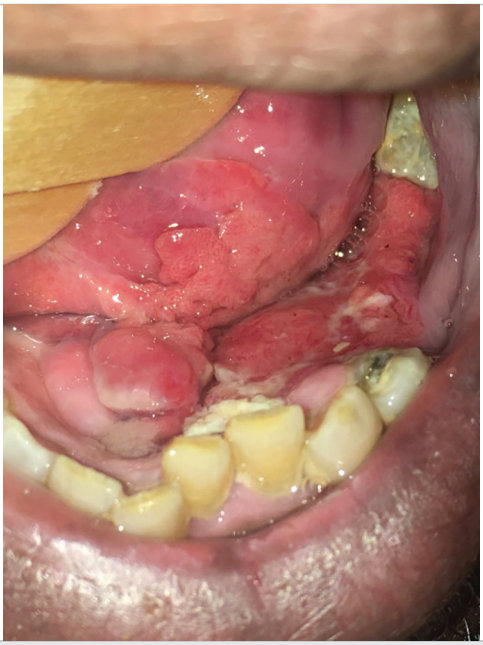

Fig. 1.3 Ventral tongue and floor of mouth squamous cell carcinoma.

mucosal and bony extent, is relatively cost-effective, and often readily available. An MRI is a useful adjunct in tumors with concern for perineural spread. PET alone has been shown to be more sensitive and specific than other imaging modalities in detecting primary and locally recurrent head and neck cancers.[60] PET/CT has the added benefit of improved localization and correlation with anatomic findings, and it can be useful in the detection of unknown or synchronous primaries or in diagnosing distant metastases. PET/CT has been shown to be extremely useful in the staging and management of advanced head and neck cancer, and its use continues to become more prevalent.[61]

Biopsy

A tissue sample is essential for the diagnosis of an oral cavity lesion. Surgical biopsies can be taken in the clinic under local anesthesia or in the operating room for select patients. Any ambiguous regional or distant lesions will also need histopathologic diagnosis, more commonly obtained by either fine needle aspiration (FNA) or core biopsy. The most common histologic diagnosis is squamous cell carcinoma, representing 90% of oral cavity cancers.[62] Other variants include adenocarcinoma, mucoepidermoid of a salivary gland, cutaneous basal cell carcinoma or melanoma of the lip, or primary tumors of the mandible.

Staging

Oral cavity cancer survival depends largely on stage at presentation, and the American Joint Committee on Cancer (AJCC) tumor node and metastasis (TNM) staging system is the gold standard. In January 2018, the AJCC 8th edition was enacted with significant alterations in both T and N staging for oral cavity cancer (▶ Table 1.1). T1 through T3 staging is still primarily dependent on tumor size, and T4a and T4b tumors are now described as “moderately advanced” and “very advanced,” as opposed to “resectable” and “unresectable.” Depth of invasion

Table 1.1 AJCC 8th edition T stage

Tx	Cannot assess
Tis	Carcinoma in situ
T1	≤ 2 cm, depth of invasion (DOI) ≤ 5 mm
T2	≤ 2 cm, DOI: 5–10 mm OR: 2–4 cm, DOI ≤ 10 mm
T3	Tumor > 4 cm OR DOI > 10 mm (and not T4)
T4a	Moderately advanced: (lip) invades bone, involves floor of mouth, inferior alveolar nerve, or skin (oral cavity) invades adjacent structures only (mandible or maxilla, maxillary sinus, facial skin)
T4b	Very advanced: invades masticator space, pterygoid plates, or skull base, or encases carotid

Table 1.2 AJCC 8th edition N stage

pNx	Cannot assess
pN0	No nodes
pN1	1 node ≤ 3 cm, extranodal extension (ENE) negative
pN2a	1 node ≤ 3 cm, ENE positive, OR 1 node 3–6 cm, ENE negative
pN2b	Multiple nodes ≤ 6 cm, ENE negative
pN2c	Bilateral or contralateral nodes ≤ 6 cm, ENE negative
pN3a	Node > 6 cm, ENE negative
pN3b	1 node > 3 cm, ENE positive, OR multiple nodes (ipsilateral, bilateral, or contralateral) with any ENE positive

(DOI) has also been added for its prognostic value. Regardless of its size, a tumor with DOI of 5 to 10 mm is automatically staged as a T2, and DOI greater than 10 mm changes the stage to a T3. Additionally, N staging continues to rely on lymph node number and size. However, both the clinical staging and pathological N staging now include assessment of extranodal extension (ENE). As demonstrated in ▶ Table 1.2, ENE positivity upstages a lymph node less than 3 cm from N1 to N2a and all other nodal stages to N3c.[63]

1.5 Anatomic Considerations/ Relevant Anatomy

The oral cavity primarily serves as the entrance to the aerodigestive tract. Eating and digestion begin in the oral cavity, with emphasis on mastication, salivation, and bolus propulsion to the pharynx. It also serves as the key site for speech modification, a respiratory conduit for inspiration, and a chemosensory organ for taste.

1.5.1 Anatomic Subsites

The oral cavity includes the following eight anatomic subsites: the lips, the upper and lower alveolar ridges and gingiva, the hard palate, the floor of mouth, the buccal mucosa, the oral tongue (the anterior two-thirds), and the retromolar trigone.[64] Having an intimate knowledge of adjacent anatomical structures is extremely important in order to perform a safe, negative margin resection and to be able to counsel the patients appropriately before treatment. The oral cavity is bounded by the vermillion border anteriorly, the buccal mucosa laterally, the hard and soft palate junction superiorly, the anterior tonsillar pillar and circumvallate papillae posteriorly, and the floor of mouth inferiorly.

Oral cavity mucosa is lined with stratified squamous epithelium, which consists of multiple layers of adherent epithelial cells. Due to their close proximity, they are well adapted to resist daily mechanical and chemical insults, and the outer layer frequently sloughs off and is replaced by the deeper layer. Frequent replacement of cells and associated proliferation and turnover increases the likelihood of development of cellular anomalies and subsequent carcinogenesis in the setting of endogenous or exogenous insults.[65] In general, thinner nonkeratinized mucosa within the oral cavity undergoes higher rates of proliferation and mitosis, which correlates with a higher incidence of carcinoma. Specifically, the floor of mouth, ventral tongue, and buccal mucosa subsites have the longest S phase of mitosis, in contrast with the palate and dorsal tongue.[66] As expected, these areas have been found to correlate with a higher incidence of malignant transformation/carcinoma.[67]

1.5.2 Muscular Anatomy

There are four bilateral pairs of muscles of mastication: the masseter, temporalis, medial pterygoid, and lateral pterygoid muscles. The masseter is the workhouse of the muscles of mastication, acting to elevate and protrude the mandible. It originates and inserts at the zygomatic arch and mandibular ramus, respectively. The temporalis muscle is a large, fan-shaped muscle that originates at the temporal fossa, extends under the zygomatic arch, and inserts on the coronoid process of the mandible. It serves to elevate and retract the mandible. The bulk of the medial pterygoid muscle originates from the medial surface of the lateral pterygoid plate and inserts onto the medial mandibular ramus and angle, joining the masseter to form the pterygomasseteric sling. It functions to elevate and weakly protrude the mandible and assist with excursion. The lateral pterygoid muscle has two heads: the superior runs from the greater wing of the sphenoid to the temporomandibular joint capsule and the inferior runs from the lateral surface of the lateral pterygoid plate to the condylar surface of the mandible. It primarily protrudes the mandible, assists with excursion, and is the only muscle of mastication to depress (or open) the jaw. Tumor invasion of the lateral pterygoid can lead to significant trismus.

The paired extrinsic tongue muscles are anchored to bone and act to protrude, retract, and allow horizontal movement of the tongue. The genioglossus, hyoglossus, and styloglossus function within the oral cavity, while the palatoglossus contributes to movement of the base of the tongue. The genioglossus extends from the mandibular mental spine to the hyoid and ventral tongue and is the major contribution to tongue protrusion. The hyoglossus originates from the greater cornu and side of the body of the hyoid, inserting onto the lateral tongue and acting to depress and retracting the tongue. The styloglossus arises from the styloid process and the stylomandibular ligament and inserts on the anterolateral and anterior tongue surface. This muscle depresses and elevates the tongue.

The paired intrinsic tongue muscles include the superior and inferior longitudinal, transverse, and vertical muscles and are

generally thought to control the tongue's shape and displacement. They form a "meshlike structure" without clear demarcation of tissue planes between them.[68] As a result, a tongue malignancy can easily spread within the intrinsic tongue musculature. It is important to keep this anatomy in mind when performing a margin-negative tumor resection.

The four paired suprahyoid muscles (digastric, stylohyoid, geniohyoid, and mylohyoid) generally act to elevate the hyoid bone and assist with swallowing. The mylohyoid is an important landmark as the inferior border of the oral cavity, separating the sublingual and submandibular spaces. These two spaces communicate via the posterior free border of the mylohyoid, allowing potential spread of infection or malignancy from the floor of mouth to the neck.

1.5.3 Dentition

Teeth are composed of enamel, pulp, dentin, and cementum. The cementum covers the dental root and is bound to the alveolar bone by specialized connective tissue called periodontal ligaments (PDLs). Periodontal disease from poor oral hygiene is very common and can lead to chronic inflammation, a major risk factor in development of oral cavity cancer.[69] Mucosal tumors can spread to the alveolus and mandible by direct extension through exposed PDLs.

1.5.4 Innervation and Taste

The mandibular nerve is the third branch of the trigeminal nerve and itself branches into the lingual nerve and the inferior alveolar nerve, terminating in the mental nerve. The mandibular nerve and its branches provide general sensation to the lower half of the oral cavity, including the mandibular dentition and PDLs, oral tongue, floor of mouth, buccal mucosa, lower lip, and all four pairs of masticator muscles. The second branch of the trigeminal nerve, the maxillary nerve, provides general sensation to the upper half of the oral cavity. Motor function of the paired extrinsic (excluding the palatoglossus) and intrinsic tongue muscles is supplied by the hypoglossal nerve.

The dorsal tongue is covered with three types of lingual papillae: circumvallate, fungiform, and filiform. They each contain hundreds of taste buds that supply afferent taste sensation to the chorda tympani branch of the facial nerve.

1.5.5 Salivary Glands

Saliva is a very important part of oral hygiene and barrier protection and is secreted from the six major salivary glands bilaterally as well as the hundreds of minor salivary glands. Salivary mucin is known to bind to the surface of oral mucosa in order to hydrate, lubricate, and protect against microorganisms, along with antimicrobial peptides.[70,71] The paired parotid glands secrete mainly serous, stimulated saliva through ducts that pierce the buccinator and open into the mouth adjacent to the maxillary second molar. The paired submandibular glands secrete the majority of mucous, unstimulated saliva through bilateral ducts at the anterior floor of mouth. They are divided into superficial and deep lobes by the mylohyoid muscle. The two smallest named salivary glands are the sublingual glands. They secrete mixed serous and mucous saliva and are located in the lateral superficial floor of mouth, adjacent to the mandibular canines.

1.6 Treatment Considerations and Approaches

Primary surgical resection is the preferred treatment for oral cavity cancer, followed by adjuvant radiation therapy and/or chemotherapy in indicated cases and based on pathologic features.[72] Definitive doses of radiation therapy have been shown to lead to an unacceptable rate of mandibular osteoradionecrosis (ORN).[73] As a result, definitive chemoradiation therapy (CRT) is generally reserved for poor surgical candidates due to unresectable tumor burden or underlying comorbidities.

1.6.1 Surgical Options and Approaches

Primary Tumor

The primary surgical objective for treatment of a head and neck cancer with curative intent is a margin-negative resection. The extent of resection depends on the location of the primary tumor, which often involves vital structures within the head and neck. No strict definitions exist for recommended surgical margins in oral cavity tumors, but multiple studies have shown a significant difference in locoregional recurrence and survival (disease free or overall) with a margin greater than 5 mm.[74–76] Intraoperatively, the surgeon often makes this assessment tactilely and sends surgical margins for frozen histologic confirmation. In advanced-stage tumors, a composite resection involving soft tissue and adjacent bone is often indicated. The bony maxilla and mandible form the framework of the oral cavity, so any oral cavity malignancy will eventually involve bone if left untreated. Bony margins are more difficult to ascertain, as the technology to rapidly decalcify bone for frozen histologic analysis is not currently available. Various methods of obtaining bony margins have been described, including bone marrow scrapings and thin cortical bone margins by osteotome, but none have yet been widely adopted.[77,78] Composite extirpation of an oral cavity cancer may require partial maxillectomy or a rim versus segmental mandibulectomy for clear margins.

Neck Treatment

The most important prognostic factor in oral cavity cancer is the presence of nodal metastasis. Surgical treatment of a clinically N0 neck relies on the probability of occult nodal metastasis, while treatment of an N+neck is absolutely indicated. Selective neck dissection (or modified radical) is now considered the standard of care, in comparison with the more historical radical neck dissection. In a lateralized oral cavity cancer, the nodal basins most at risk are the ipsilateral levels I through III.[79,80] Per the decision tree analysis performed by Weiss et al in 1994, risk of occult nodal metastasis greater than 20% in any head and neck cancer warrants elective treatment of the neck.[81] This threshold continues to be the prevailing opinion today.

Advanced tumor stage, aggressive pathologic features, and immunocompromised status are among the major indicators

for performing an elective neck dissection. For those patients with lower risk of occult nodal disease, surgical treatment of the neck is helpful for both prognostic value and guiding the decision for adjuvant therapy. Multiple retrospective studies have illustrated that primary tumor thickness of at least 3 to 4 mm is correlated with increased risk of cervical nodal metastasis.[82–84] More recently, a randomized control trial by D'Cruz et al., demonstrated a significantly increased rate of overall and disease-free survival in those patients with greater than 3.0 mm tumor depth who had elective neck dissections. The results demonstrated a 3-year 13% overall survival advantage in early-stage oral cancer patients with tumor depth greater than 3 mm who underwent elective versus therapeutic neck dissection.[85] Primary tumors of the floor of mouth tend to exhibit more frequent regional spread due to their proximity to neurovascular structures. Therefore, T1 lesions or greater warrant an elective neck dissection.[86]

Sentinel lymph node (SLN) biopsy is an effective, minimally invasive option for identifying occult nodal metastasis in early oral cavity cancers (cT1–T2). It can detect aberrant nodal drainage from the primary tumor while reducing the need for a potentially unnecessary elective neck dissection. It can also be used in patients with lower but not negligible risk of occult nodal disease, as in primary lip cancers.[87] According to a recent review and meta-analysis of over 3,500 cT1–T2 patients, SLN biopsy had a pooled identification rate of 96.3%, sensitivity of 87%, and negative predictive value of 94%.[88] With the appropriate surgical technique and experience, the head and neck cancer surgeon should consider SLN biopsy as an alternative to elective neck dissection in selective early oral cavity cancers.

Reconstructive Options

Head and neck ablative defects require consideration of both structure and function and are therefore uniquely challenging for the head and neck reconstructive surgeon. General principles adhere to the reconstructive ladder, with use of secondary intention, primary closure, skin grafts, local flaps, regional flaps, or free flaps. Unlike other anatomic areas, the head and neck often require a combination of reconstructive techniques to appropriately address the needs of a specific ablative defect. It is important to address concerns with oral intake, speech, breathing, aesthetics, and tissue coverage of vital structures (i.e., carotid artery or dura). Goals of reconstruction are a critical component of discussion with patients, and planning should be coordinated with appropriate multidisciplinary care providers. Development of free tissue transfer has markedly improved the functional and cosmetic outcomes for head and neck cancer patients with large, composite defects, and they should be considered in the appropriate patients[89] (▶ Fig. 1.4, ▶ Fig. 1.5, ▶ Fig. 1.6).

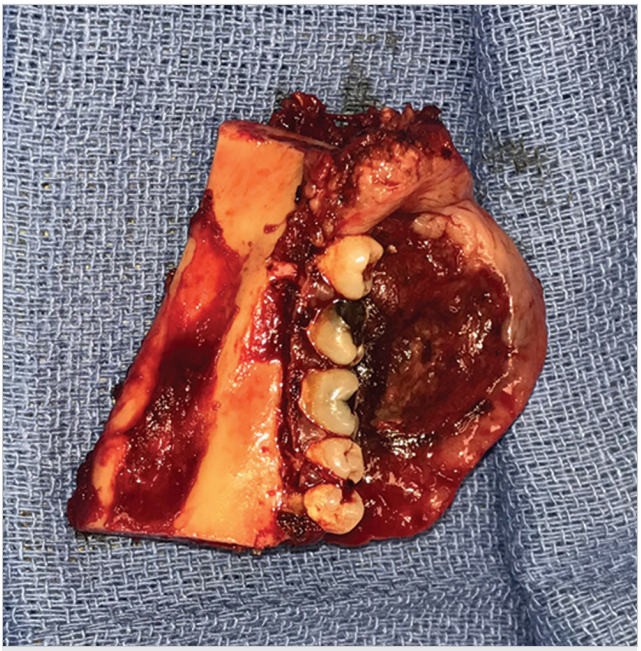

Fig. 1.5 Composite resection.

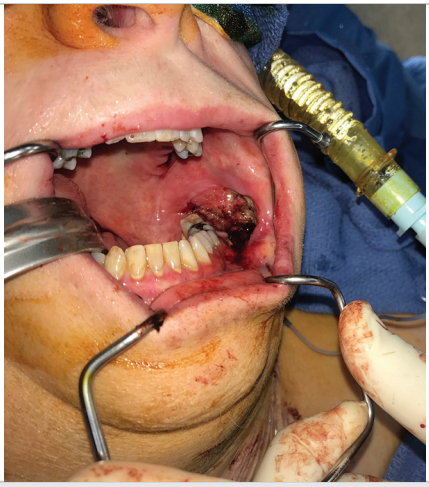

Fig. 1.4 Buccal mucosa squamous cell carcinoma invading the mandibular gingiva and alveolar ridge cortex.

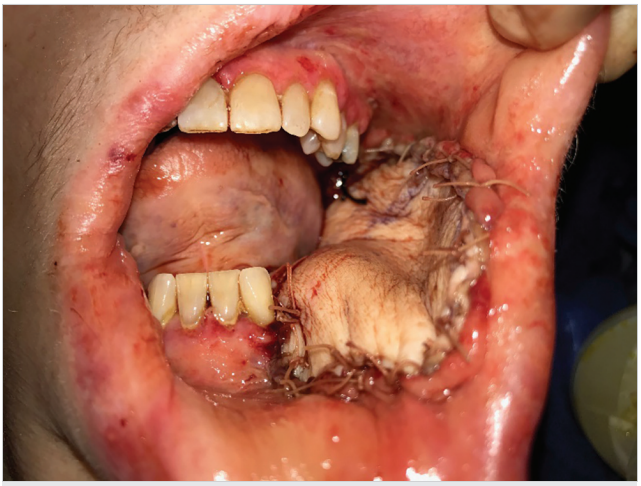

Fig. 1.6 After reconstruction with a fibular free flap.

1.6.2 Medical Options

Radiation and Chemotherapy

Surgery is the preferred treatment for oral cavity cancer; thus, radiation therapy and/or chemotherapy are generally utilized in the postoperative adjuvant setting. Postoperative radiotherapy (PORT) is recommended for advanced tumor stage III–IV and positive nodal disease.[72] The addition of concurrent chemotherapy is reserved for positive tumor margins or ENE, as adjuvant CRT has shown to significantly improve disease-free survival and locoregional control in those patients when compared to PORT alone.[90,91] Appropriate adjuvant dosage for optimizing locoregional control while minimizing toxicity is generally 60 Gy, and it should be administered within 6 weeks postoperatively.[92,93]

Radiation and chemotherapy primarily target and damage proliferating and differentiating cells, causing oral mucosa to become thin or ulcerated.[65] These effects can be seen especially in those thinner nonkeratinized areas, namely, the floor of mouth, buccal mucosa, and ventral tongue, causing mucositis and ulceration. These lesions can lead to pain, dehydration, and poor nutritional status that occasionally requires enteral feeding. Radiation permanently decreases proliferation in all affected tissues and degrades their normal matrices, endothelial cells, and fibroblasts. As a result, radiated tissues have increased fibrosis and ischemia, presenting clinically with trismus, fistula formation, tissue necrosis, and infection. Toxicity effects are exponentially related to the total dose of radiation.[92] Adding concurrent chemotherapy augments the rate of acute adverse toxicity and has even led to death.[94] When counseling patients on the risks and benefits of adjuvant therapy, it is important to have an honest discussion about the survival advantages as well as the tissue toxicities.

Multimodality, Multidisciplinary Therapy

Multimodality therapy is often the treatment of choice for advanced-stage oral cavity cancer. Multidisciplinary treatment refers to the coordination of multiple specialists for the care of a patient. Addressing the oncologic and quality-of-life needs of a head and neck cancer patient is complex. Effective care requires the input of head and neck surgery, medical oncology, radiation oncology, radiology, pathology, audiology, oral surgery, prosthodontic dentistry, speech pathology, and nutrition. Multiple tertiary academic centers now have multidisciplinary clinics to streamline the patients' numerous clinic visits, ultimately aiming to decrease time to treatment and improve overall completeness of care.[95] A recent study even showed an increase in oropharyngeal disease–specific survival with implementation of a multidisciplinary clinic for patients treated with definitive CRT.[96] For definitive surgical patients, one of the most pressing time constraints is to initiation of adjuvant therapy within the recommended postoperative 6 weeks. Expediting postoperative care is crucial, as delay to adjuvant treatment is associated with decreased survival.[97]

1.7 Surgical Sequelae

Surgical sequelae fundamentally include the outcomes after completion of ablation, reconstruction, and possible adjuvant therapy. It is challenging to delineate independent effects of each step of treatment, as they rarely occur in isolation. Patients with lip tumors develop concerns with oral competence and microstomia. Tongue defects impair speech articulation and bolus propulsion necessary for swallowing. Buccal tumors can lead to considerable trismus. Tumors involving the mandible have a significant impact on mastication and occlusion. Hard palate tumor resection and reconstruction may result in velopharyngeal insufficiency or oronasal fistula formation. Immediate postoperative edema often necessitates tracheostomy tube placement at the time of surgery to prevent airway compromise. All subsites of oral cavity cancer can lead to significant changes in physical appearance.

1.7.1 Long-Term Sequelae/ Rehabilitation

Survivors of head and neck cancer often live with long-term sequelae of radiation and/or chemotherapy in addition to surgery. Postradiation dental caries or periapical abscesses sometimes necessitate dental extraction, and development of mandibular or maxillary osteoradionecrosis is a known complication. These patients can benefit from pre- and post-extraction hyperbaric oxygen and should be treated by dentists or oral surgeons familiar with head and neck cancer patients.[98] Xerostomia and trismus are exceedingly common and lead to dysgeusia, dysphagia, malnutrition, and poor overall quality of life. As a result, patients sometimes require placement of an enteral feeding tube. Treatment of trismus includes jaw exercises and rehabilitation or mechanical stretching in the operating room. Persistent oronasal or oroantral fistulas can be managed surgically or with a prosthodontic palatal obturator. Speech concerns can be addressed by a specialized speech and language pathologist during individualized speech therapy sessions. Development of neck lymphedema is a very common complication due to impaired lymphatic drainage. It can cause stiffness and even swallowing difficulties, with significant improvements after physical therapy and manual lymphedema massage.[99] An often overlooked sequela is a strong association between head and neck cancer survivors and depressive mood.[100] Dysfunctions in eating and salivating are almost universal after oral cavity cancer treatment, and they are major risk factors for development of depression.[101] These patients may benefit from seeking counseling or attending survivorship meetings. Again, utilizing multidisciplinary care is paramount to your patient's overall functional status and can significantly impact both quality of life and survival.[102]

Key Points

- Oral cavity lesions are heterogeneous in appearance and symptomatology.
- Workup includes a histologic tissue diagnosis and appropriate imaging (CT or MRI with possible PET/CT).
- Definitive surgery ± adjuvant therapy is the mainstay of treatment.
- Primary tumor depth greater than 3 mm or floor of mouth tumors T1 or greater necessitates an elective neck dissection in the N0 neck.

- Consider an SLN biopsy in early-stage tumors.
- Head and neck reconstruction is very challenging and sometimes requires more than one reconstructive technique to optimize functional and aesthetic outcomes.
- Multidisciplinary care increases survival.

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2 Patient Populations at Increased Risk for Oral Cavity Cancer

Kevin M. Motz and Marietta Tan

Summary
Oral cavity cancer occurs more frequently in certain geographic areas and patient populations. In some regions of the world, higher rates of oral cancer are attributable to frequent usage of tobacco, alcohol, and betel quid. Furthermore, patients with either specific genetic predispositions or acquired immunosuppression are also at increased risk for the development of oral cancer. This chapter will review those populations at greater risk for oral cavity cancer.

Keywords: betel quid, fanconi anemia, dyskeratosis congenita, xeroderma pigmentosum, epiderma bullosis, immunosuppression

2.1 Introduction

Oral cavity cancer (OCC) comprises the group of neoplasms that present within the confines of the vermillion border of the lips anteriorly and the circumvallate papillae and the junction of the hard and soft palates posteriorly. OCC is a significant problem worldwide, with peaks in its incidence occurring both in specific geographic regions and in individual patient populations. The most common type of OCC is squamous cell carcinoma (SCC), but other malignant tumors arising from epithelial or mesenchymal tissues can occur. While the overall incidence of OCC is relatively low, areas such as France, Brazil, and South Asia have increased rates of the disease. In addition, OCC is more common in specific at-risk patient populations that have either genetic predispositions or underlying chronic acquired or iatrogenic immunosuppression. The geographic locations and populations at increased risk for OCC will be discussed in this chapter.

2.2 Geographic Variation in OCC Incidence

OCC has a global incidence ranging from 0.4 to 23.1 cases per 100,000 individuals, with an estimated 275,000 new cases of OCC diagnosed each year.[1,2] OCC is more common in men, and the risk of malignancy increases with age.[2] SCC accounts for up to 95% of oral cavity malignancies, while sarcomas, lymphomas, salivary gland tumors, and melanomas account for the remainder of cases.[3–6]

The incidence of OCC varies considerably by geographic region, a phenomenon attributed to disparate rates of exposure to tobacco, alcohol, and other modifiable risk factors.[7] In most industrialized nations, the overall incidence of OCC is declining, secondary to a decrease in the use of tobacco products, a major risk factor for SCC.[8,9] For example, in much of North America, Australia, and Western Europe with the exception of France, the incidence of OCC is relatively low, ranging from 0.4 to 4 cases per 100,000 individuals. However, the incidence of OCC in France is exceedingly high, with 42.3 cases per 100,000 male individuals.[2] The increased incidence of OCC in France is related to the increased use of tobacco and alcohol, which can increase risk of OCC by up to 3,800%.[10] In Brazil, which is commonly cited as having a high incidence of OCC, the majority of cases are clustered in the southern and southeastern regions of the country. The concentration of cases in those regions is attributed to higher rates of tobacco use, as well as lower socioeconomic status and reduced access to health care services.[11] Finally, the developing countries of India, Pakistan, Sri Lanka, and Bangladesh have some of the highest rates of OCC in the world, with incidences of up to 9 to 11 cases per 100,000 individuals.[9] In these countries, OCC accounts for up to 25% of new cancer diagnoses[2] and is associated with high rates of tobacco, alcohol, and betel quid usage.

2.2.1 Betel Quid Chewing

Betel quid chewing represents a modifiable risk factor that increases the risks of both oral premalignant lesions and OCC. “Betel quid” refers to combinations of betel leaf, areca nut, and slaked lime, with or without the addition of tobacco leaf, which is then chewed or packed into the gingivobuccal sulcus of the mouth. Various combinations of these ingredients can be made into betel quid, or each ingredient can be consumed individually.[12] Sweeteners and essences, such as menthol, are also commonly added to betel quid. Betel quid formulations are highly variable by region and may have different designations based on composition. Mass-produced betel quid substitutes, known as pan masala (which does not contain tobacco) and gutka (which contains tobacco), are also widely available.[13] Given the variability in content, when the term “betel quid” is used, it is important to determine the formulation’s specific components. In particular, the addition of tobacco further increases the risks of betel quid. For example, a meta-analysis of 25 studies from the Indian subcontinent showed a relative risk of OCC of 8.47 for betel quid with tobacco, compared to 2.41 for betel quid without tobacco.[14] It is also important to note that the concomitant use of alcohol or cigarette smoking with betel quid chewing increases the risks of oral premalignancy and OCC in a synergistic manner.[15,16]

Global estimates of betel quid use indicate that there are currently nearly 700 million consumers worldwide.[12] The chewing of betel quid in different forms, a custom which dates back thousands of years, has become deeply ingrained in a number of sociocultural traditions. The earliest use of betel quid as a masticatory object dates back to 430 BC. Indian scripts dating back to the 4th century indicate that betel quid was originally thought to be a therapeutic agent and was used to treat a wide range of human disease. It was also recognized for its euphoric and stimulant effects.[17] The highest rates of betel quid use are clustered in the countries of India, Pakistan, Bangladesh,

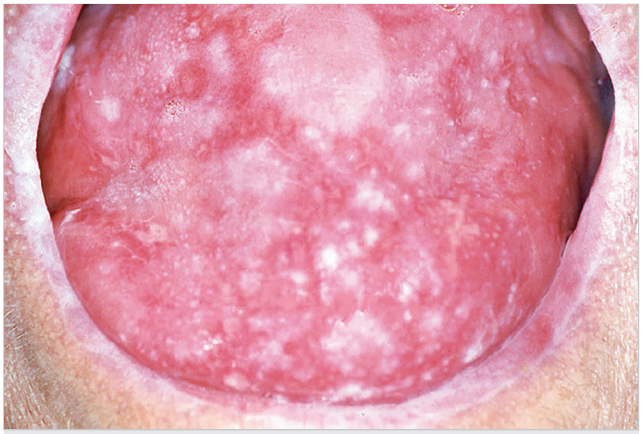

Fig. 2.1 Oral submucous fibrosis affecting the tongue. (Source: Laskaris G, ed. Color Atlas of Oral Diseases. Diagnosis and Treatment. 4th ed. New York, NY: Thieme; 2017.)

Sri Lanka, and Taiwan. In these areas, up to 40% of the population use betel quid in various forms.[18]

Premalignant oral lesions associated with the use of betel quid include leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus.[12,19,20] The presence of leukoplakia or erythroplakia secondary to betel quid use is common and has been associated with an increased risk of oral malignancy. Betel quid use can also lead to oral submucous fibrosis, a premalignant condition characterized by subepithelial inflammation and fibrosis (▶ Fig. 2.1). The rate of malignant transformation of oral submucous fibrosis to carcinoma has been estimated at 8% over a 17-year period. Moreover, patients with oral submucous fibrosis may be up to 400 times more likely to progress to malignancy compared to tobacco users without premalignant lesions.[12] Nonmalignant consequences of oral submucous fibrosis also exist and contribute to morbidity. Depending on the degree of fibrosis, oral submucous fibrosis can result in trismus, dysarthria, limited ability to provide oral hygiene, and limited food consumption leading to malnourishment. In particular, trismus may complicate surveillance and surgical resection of dysplastic or malignant lesions. These considerations should be taken into account when initiating treatment plans for patients with OCC secondary to betel quid use.[12,21]

In addition to increasing the risk of OCC, betel quid use also increases the risk of malignancies of the esophagus, larynx, lung, liver, and pancreas.[22] A dose-dependent relationship exists between the duration and amount of betel quid use and the risk of malignancy. Given these risks, patients who utilize betel quid should undergo increased surveillance of oral lesions, and clinicians should maintain a heightened suspicion for carcinoma. Furthermore, patients should receive counseling on the risks of use and the benefits of cessation, as the cessation of betel quid use reduces the risk of malignancy by up to half.[14]

2.3 Inherited Syndromes

The incidence of OCC is increased in patients with certain inherited syndromes. The predisposition to malignancy in these individuals can be explained by the "two-hit" hypothesis, in which the first "hit" is the inherited mutant allele, while the second "hit" is an acquired somatic mutation leading to malignant transformation.[23] Genomic instability in some patient populations may also lead to earlier and more frequent development of malignant lesions.[24] Individuals with these syndromes therefore require close surveillance to monitor for the development of premalignant or malignant oral cavity lesions. These patients should also be counseled on smoking and alcohol cessation, in order to mitigate their risk of malignancy.

2.3.1 Fanconi Anemia

Fanconi anemia (FA) is a rare, autosomal recessive disorder caused by mutations in any of at least 15 known genes, each involved in deoxyribonucleic acid (DNA) repair and stabilization pathways. Defects in these pathways lead to chromosomal instability and thereby increase the risk of malignancy, including lymphocytic and myelocytic cancers, as well as solid organ tumors.[25] FA is also characterized by bone marrow failure and sensitivity to DNA cross-linking agents. Acute myeloid leukemia is the most common malignancy associated with FA. However, as the life expectancy of FA patients has improved due to advances in leukemia management, the incidence of solid organ tumors has risen to as high as 28% by 40 years of age.[26] Solid tumors in FA patients occur most commonly in the head and neck, the majority of which arise in the oral cavity. The incidence of head and neck SCC is 240- to 700-fold greater in FA than in the general population,[27–29] and OCC comprises over two-thirds of head and neck cancers diagnosed in FA.[30]

In individuals with FA, OCC and other head and neck cancers are known to be aggressive and carry a poor prognosis.[26] The propensity of FA patients to develop OCC, coupled with poor tolerance of radiation therapy and chemotherapy, underscores the need for careful and frequent screening, starting as early as late childhood, in this population.[26,30]

2.3.2 Dyskeratosis Congenita

Dyskeratosis congenita (DC) is a rare inherited disorder caused by defects in telomere maintenance. The most common form of DC is X-linked recessive, but autosomal dominant and autosomal recessive forms have been observed.[31] Clinically, it is characterized by bone marrow failure, premature aging, and increased risk of malignancy. Patients with DC present with a triad of mucocutaneous findings: oral leukoplakia, reticulated hyperpigmentation of the skin, and nail dystrophy. Leukoplakia affects up to 80% of patients with DC and most commonly affects the oral mucosa (▶ Fig. 2.2).[32] The leukoplakia associated with DC can affect any mucosal subsite within the oral cavity and is considered a premalignant condition.[31] Secondary to the increased propensity for oral leukoplakia, the risk of OCC is significantly increased in DC, with an incidence of tongue cancer 1,154-fold greater in patients with DC than in the general population.[33] Given the increased frequency and early onset of premalignant mucosal changes in DC, up to 35% of oral cancer malignancies arise in the third to fifth decades of life in these patients. Individuals with DC therefore require close surveillance of leukoplakic lesions, to ensure early detection and treatment of malignancy.[34]

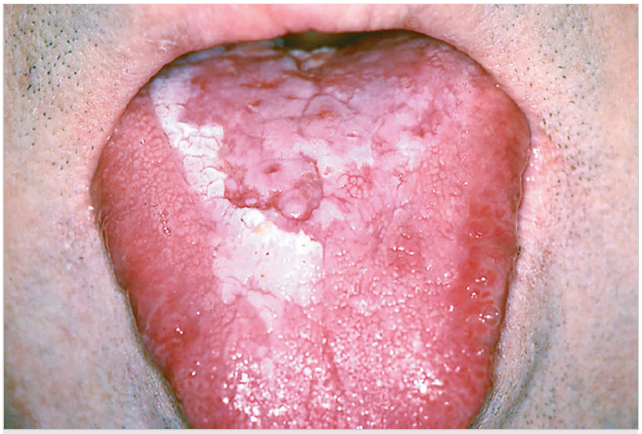

Fig. 2.2 Leukoplakia on the dorsum of the tongue in a patient with dyskeratosis congenita. (Source: Laskaris G, ed. Color Atlas of Oral Diseases. Diagnosis and Treatment. 4th ed. New York, NY: Thieme; 2017.)

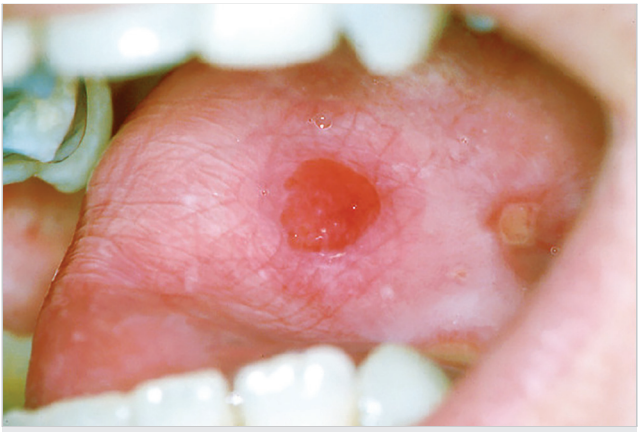

Fig. 2.3 Bulla formation on the tongue in a patient with epidermolysis bullosa. (Source: Laskaris G, ed. Color Atlas of Oral Diseases. Diagnosis and Treatment. 4th ed. New York, NY: Thieme; 2017.)

2.3.3 Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is a rare, autosomal recessive disorder characterized by hypersensitivity to ultraviolet radiation, secondary to defective nucleotide excision repair mechanisms.[23] Individuals with XP are at increased risk of developing skin cancers, with 50% of patients developing cutaneous malignancies between the ages of 10 and 14 years. The majority of malignancies associated with XP occur on the face, scalp, lips, and eyelids. However, other sites, such as the oral tongue or gingiva, can be affected. SCC affecting the anterior tongue, presumably resulting from sun exposure to the tip of the tongue, is estimated to occur over 20,000-fold more frequently in XP patients under the age of 20 compared to the general population. In addition, malignant neoplasms arising from oral cavity sites other than the tongue occur 400 times more frequently in young XP patients than in the general population.[35,36] Patients with XP therefore require close surveillance with frequent and thorough examination of the skin, lips, and oral cavity. Early identification and treatment of premalignant or malignant lesions are imperative.

2.3.4 Epidermolysis Bullosa Spectrum

Epidermolysis bullosa (EB) is a spectrum of diseases hallmarked by blistering and mechanical fragility of the skin. There are four main types of EB: intraepidermal, junctional, dermolytic, and mixed. In addition, there are over 30 subtypes of EB.[37] The clinical presentation of EB can be highly variable and reflects the marked genetic heterogeneity among subtypes in this disease spectrum. The presentation and severity of oral manifestations in EB differ by type or subtype of disease, but patients commonly present with multiple intraoral bullae that rupture, leading to ulceration and erosion (▶ Fig. 2.3). Multiple cases of OCC, most commonly affecting the tongue, have been reported in individuals with EB who survive the second and third decades of life. Patients with generalized recessive dystrophic EB therefore need close monitoring of oral lesions.[38–41]

2.4 Acquired Immunosuppression and Immune Dysregulation

A functional immune system is thought to play a protective role in preventing tumor development. The theory of immune surveillance, first proposed by Burnet in 1970, states that thymic-dependent effector lymphocytes play a role in the elimination of developing cancers.[42] This process may be diminished in patients with acquired immunosuppression, thereby allowing the development of certain malignancies. These malignancies include lymphomas, Kaposi's sarcoma, renal cell cancer, hepatobiliary cancers, and SCC of the skin, cervix, and anogenital region.[42–44] In OCC, a similar immunologic etiology has been observed. Immunosuppressed patients have a reported 2- to 15.7-fold increased risk of developing an oral malignancy.[45] Increased incidences of OCC have been reported in patients that are immunosuppressed secondary to human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), solid organ transplantation (SOT), hematopoietic stem cell transplantation (HSCT), and graft-versus-host disease (GVHD). However, the risk of specific associated malignancies varies based on the etiology of immunosuppression.

2.4.1 Human Immunodeficiency Virus

HIV is a lentivirus that can lead to AIDS. HIV infects $CD4^+$ T lymphocytes and other immune cells, resulting in the eventual depletion of $CD4^+$ T cells and the loss of cell-mediated immunity.[46] Immunosuppression secondary to HIV leads to an increased propensity for disease-specific infections, as well as an increased risk of specific malignancies, including OCC. There is a 2.3-fold increased incidence of cancers of the oral cavity and pharynx in patients with HIV/AIDS compared to the general population.[47] The relative risk of developing OCC in HIV/AIDS increases as $CD4^+$ T-cell counts decline, and evidence suggests that restoration or maintenance of immune competence with antiretroviral therapy can reduce the risk of malignancy.[48] HIV/AIDS patients who develop premalignant oral

lesions should be closely monitored. In addition, patients should be counseled on cessation of modifiable risk factors such as tobacco and alcohol use, in order to mitigate the risk of oral malignancy.

2.4.2 Solid Organ Transplantation

Suppression of the immune system to prevent rejection is a critical component in the management of SOT. However, immunosuppression is known to increase the risk of de novo malignancies, including OCC,[49] by weakening immune surveillance and worsening susceptibility to oncogenic viral infections. In patients with SOT, there is a 5.5-fold increased risk of OCC, with a 10.7-fold increased risk for malignancy specifically of the tongue.[50] The risk of developing cancer at different primary sites also varies depending on the transplanted organ. For example, the incidence of OCC is up to 10-fold higher in liver transplant recipients compared to the general population, but only fourfold to fivefold higher in kidney, heart, or lung transplant recipients.[49,51]

The specific risk of malignancy in patients with SOT appears to be related to the duration and degree of immune suppression and does not appear to be agent specific.[52,53] SOT patients who develop OCC have worse survival rates at 1 year compared to nontransplanted patients with OCC.[54] Furthermore, treatment of head and neck malignancies in this population may be complicated by the need for ongoing immunosuppression to ensure transplant viability. Due to the propensity for worsened survival and locoregional control in SOT patients with head and neck cancer, identification and treatment of oral cavity malignancies at an early stage is critical.[51,55] These outcomes highlight the importance of continued surveillance in patients who have undergone SOT.

2.4.3 Hematopoietic Stem Cell Transplantation/Chronic Graft-versus-Host Disease

HSCT is a curative therapy for the management of multiple malignant and nonmalignant hematological disorders. The frequency of HSCT has steadily increased over the past 30 years.[56,57] It is now well recognized that patients who have undergone HSCT have an increased risk for the development of secondary solid organ tumors, with a 2.7-fold increased incidence of all solid tumor types when compared to the general population. The risk is significantly higher for oral cavity malignancies, with a 19.5-fold increased risk of tongue cancers and a 12.5-fold increased risk of cancers of the gum or other sites in the oral cavity. In addition, the risk of developing OCC after HSCT increases over time, thereby placing younger HSCT patients in a higher risk category.[58]

The increased risk of OCC in this patient population has been attributed to chronic graft-versus-host disease (cGVHD), a sequela of HSCT that occurs in 60 to 80% of long-term survivors. Chronic GVHD results when transplanted donor T lymphocytes mount an immune response against recipient tissue, due to differences in histocompatibility antigens. Oral manifestations of cGVHD result from chronic submucosal inflammation and can lead to leukoplakia, fibrosis, and lichen planus (▶ Fig. 2.4). The increased risk of OCC in patients who have undergone HSCT is attributed to the chronic inflammation associated with cGVHD; it is thought that the repeated immunologic injury predisposes the oral mucosa to malignant transformation.[59,60] In addition, patients requiring HSCT are likely to have previously undergone cytotoxic therapy with radiation or chemotherapy, thus further increasing their risk of secondary malignancy. Given the increased risk of OCC in patients with cGVHD, increased surveillance is necessary, albeit not always straightforward. Oral manifestations of cGVHD include hyperkeratosis, ulceration, erythema, and pain, all of which can make detection of secondary oral cavity malignancies more challenging.

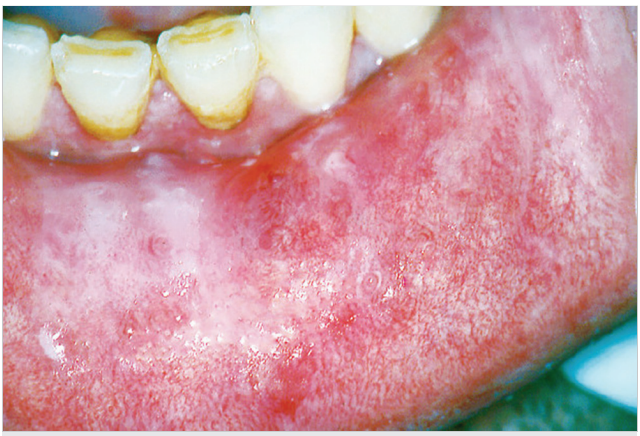

Fig. 2.4 Oral manifestation of chronic graft-versus-host disease. (Source: Laskaris G, ed. Color Atlas of Oral Diseases. Diagnosis and Treatment. 4th ed. New York, NY: Thieme; 2017.)

2.5 Clinical Presentation

Patients with the inherited syndromes described above often present with OCC at younger ages and in the setting of other mucosal disease. In particular, individuals with XP develop OCC at very young ages compared to the general population, with most patients presenting before 20 years of age.[35,36] Individuals with FA and DC also develop OCC at young ages. One study found that FA patients developed OCC at a mean age of 32 years, compared to 63 years in the general population.[26] Similarly, patients with DC developed SCC of the head and neck at a median age of 32 years.[33] Furthermore, in patients with inherited syndromes such as FA, OCC often develops in the absence of a history of tobacco and alcohol use, which are common risk factors for oral cancer in the general population.[26] These individuals may present with more advanced cancers at initial diagnosis compared to the general population.[28]

Patients with acquired immunosuppression due to either SOT or HSCT may also develop OCC at younger ages than the general population and without exposure to other risk factors like tobacco or alcohol.[51,60] After SOT, the mean time to diagnosis of noncutaneous head and neck cancer is 7.8 years, though the mean interval is shortest in liver transplantation (27 months) and as long as 14 years in kidney transplantation.[51,61] The time to diagnosis of OCC after the development of cGVHD in HSCT likewise ranges from 2 to more than 10 years.[60]

2.6 Treatment Considerations

Individuals who develop OCC in the setting of inherited syndromes or acquired immunosuppression must be given special consideration when planning treatment. These patients should be managed within a multidisciplinary setting. The underlying etiology of the disease process, the patient's functional and immune status, and the use of previous cytotoxic therapies should be considered.

In general, the primary treatment modality in OCC is surgical resection with or without adjuvant radiation and chemotherapy. Given that complete surgical resection can often produce large oral cavity defects, reconstructive options and potential wound-healing issues must be given careful consideration. A history of previous radiation, underlying immunosuppression, and hematologic dyscrasias can lead to secondary complications of surgery and should be investigated preoperatively and managed aggressively when possible.

Underlying genetic anomalies can lead to increased rates of complications from radiation or chemotherapy. In particular, the underlying DNA repair defects in FA make these patients extremely sensitive to both radiation and cytotoxic chemotherapy. Radiation therapy results in high rates of severe mucositis, dysphagia, and pancytopenia in patients with FA, and several deaths have been reported due to severe systemic complications resulting from radiation.[30] Over 40% of patients are not able to complete radiation therapy.[62] In addition, FA patients are exquisitely sensitive to cisplatin, a DNA cross-linking agent and the mainstay of current head and neck SCC chemotherapeutic regimens. Conventional chemotherapy can therefore result in significant toxicity and should be avoided in FA.[30,63] Consequently, surgery is the mainstay of treatment of OCC and other head and neck cancers in patients with FA. Surgery can be well tolerated in these patients, but preoperative assessment of bone marrow function and potential need for platelet or blood transfusion is critical.[30]

The use of chemotherapy for the management of OCC in patients who have undergone renal transplantation should also be given careful thought, due to the concern for worsening graft function. Surgical resection and radiation therapy are therefore the preferred treatment modalities for most early-stage cancers in patients who have undergone renal transplantation. However, one study of head and neck cancer after SOT found that even cisplatin-based chemotherapy was safe in kidney transplant patients, with no reported major renal toxicities.[64] In some patients, there may also be a role for judicious reduction in immunosuppression, provided there is close monitoring of graft function.[65]

2.7 Conclusion

OCC is a relatively rare malignancy, but its incidence is increased in specific at-risk populations. Individuals exposed to modifiable risk factors, such as tobacco, alcohol, or betel quid use, have increased incidences of OCC. Variable rates of exposure to these modifiable risk factors explain many of the geographic differences in OCC disease burden. In patients with significant exposure to products such as betel quid, a higher index of suspicion should be present when evaluating oral lesions. In addition, patients with specific underlying genetic abnormalities or acquired immunosuppression are at particular risk for the development of OCC. Increased screening for and surveillance of premalignant lesions is imperative in these patients.

Key Points

- While the overall incidence of OCC is low, it is elevated in specific geographic areas with increased exposure to modifiable risk factors and in specific populations with certain underlying inherited or acquired conditions.
- Increased incidences of OCC have been identified in France, Brazil, and South Asia, secondary to the increased use of tobacco, alcohol, and betel quid.
- Betel quid is the combination of betel leaf, areca nut, slaked lime, and possibly tobacco; its use has been shown to increase the risk of OCC.
- The risk of OCC is increased in patients with specific inherited conditions, including FA, DC, XP, and EB spectrum.
- Immunosuppression increases the risk of OCC in patients with HIV/AIDS, SOT, and HSCT.
- cGVHD increases the risk of OCC in patients who have undergone HSCT.

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Section II

Premalignancies of the Oral Cavity