Oral cancer (diagnosis and treatment planning)

Introduction

Squamous cell carcinoma makes up over 90% of cancers affecting the oral cavity. While sarcomas, melanomas, salivary gland tumors, lymphomas, and metastatic disease also occur in the oral cavity, they represent the minority of cases.

Worldwide oral cancer is the sixth most common malignancy, with incidence varying greatly among different geographic locations.

The use of tobacco and alcohol has been long recognized as major risk factors for the development of squamous cell carcinoma in the head and neck. Human papilloma virus (HPV) has also been found to be a major contributor to the development of oropharyngeal squamous cell carcinoma. Other risk factors include genetics, toxic exposures, diet, and environmental factors.

Unlike the treatment of cancer arising from other anatomic sites of the head and neck, the primary treatment strategy for Oral SCC remains surgery. Although multimodal therapy, including adjuvant radiation therapy (RT) with or without chemotherapy, is frequently used for advanced-stage disease, surgery remains the cornerstone in the management of Oral SCC.

Etiology of oral carcinoma

Etiology of oral SCC is multifactorial. Local irritants contribute significantly to the conversion of a premalignant process to invasive carcinoma.

The prominent risk factors are:

- **Tobacco**

Large, well-designed, population-based studies affirm the correlation between tobacco use and the risk of oral cavity cancer. Tobacco smoking is an independent risk factor; compared to nonsmokers, smokers are six to eight times more likely to develop oral cavity cancer. More than 300 chemicals in tobacco smoke have been identified as contributing to carcinogenesis. It is thought that exposure to these

carcinogens leads to malignant transformation of cells. Smoking cessation is effective in reducing risk, though not in its complete elimination.

Outside of cigarettes, both pipe and cigar smoking increase the risk for the development of oral cancer. The role of smokeless tobaccos within the United States has long been accepted to increase cancer risk, especially gingival and buccal cancers.

Other forms of chewed tobacco have been shown as independent risk factors for oral cancer. Likely the most prominent is use of tobacco and betel nut in parts of India and Southeast Asia. In one study the incidence of oral cavity cancer was 123-fold higher for individuals who smoke and chew betel nut.

Electronic cigarettes (e-cigarettes) were introduced in the early 2000s and aggressively marketed to young people as a healthier, trendy alternative to cigarettes. An e-cigarette consists of a liquid cartridge containing nicotine dissolved in propylene glycol (often with food flavoring added), a heating element, battery, and mouthpiece. Initially, the lack of carcinogenic additives was felt to reduce the user's risk of cancer compared to traditional cigarettes. More recent studies, however, have identified the carcinogen N-nitrosonornicotine in the saliva of e-cigarette users and the ability of e-cigarettes to induce DNA strand breaks and cell death independently of nicotine in vitro.

There is no evidence at the current time to support the association of marijuana use and development of oral squamous cell carcinoma (OSCC). A 2004 meta-analysis demonstrated no increased risk in a large, multi-study pooled analysis.

- **Alcohol**

Alcohol has long been considered a co-risk factor in the development of OSCC, acting synergistically with tobacco by solubilizing its toxins and concentrating them in the dependent portions of the oral cavity (OC): the floor of mouth and lateral borders of the tongue in particular. Though not a carcinogen itself, ethanol breaks down to acetaldehyde, a highly toxic metabolite responsible for DNA damage in oral mucosa.

- **Oncogenic Viruses**

A number of human viruses have been suggested as etiologic agents for oral cavity cancer through their transformation of human DNA. Herpes simplex virus type 1 (HSV-1) and human papillomaviruses (HPVs) have been reported by various authors. Although the role of HPV in oropharyngeal cancer has been established, the role of HPV in oral cavity cancer at present is controversial. HPV-6 and HPV-16 have been most commonly implicated using polymerase chain reaction (PCR) assays of human tissue.

- **Nutritional deficiencies**

Dietary deficiencies of vitamin A, folate, riboflavin, iodine, and iron add to the risk of cancer. High dietary fiber; vitamins C, E, and A; and selenium offer protection against cancer.

- **Poor oral hygiene and traumatic injury of dental origin**

Poor oral hygiene is often associated with gingivoperiodontal infections raising bacterial colony count leading to a constant inflammatory response. This together with traumatic tooth injury can lead to a carcinogenic effect.

- **There is an increased risk of oral and oropharyngeal carcinomas in those with HIV/AIDS and who have undergone organ transplant.**

There is a similar increase in cancer rates with both populations supported that immune deficiency is an independent risk factor for the development of cancer.

Precancerous Situations of Oral Cavity

Precancerous situations can be broadly divided into precancerous conditions and precancerous lesions. Precancerous condition's most commonly seen in India are oral submucous fibrosis (OSMF) and oral lichen planus. Precancerous conditions can be associated with the precancerous lesions.

Precancerous conditions make every part of the oral cavity susceptible to cancer conversion as is seen in oral submucous fibrosis (OSMF). The phenomenon simulates field cancerization. Development of a second primary despite adequate

treatment of the first is common. Sometimes two primaries at distant anatomical sites are noted in extensive long-standing OSMF.

Precancerous lesion is pathology of the oral mucosa which has a tendency to transform into the squamous cell carcinoma. The commonly prevalent lesions are leukoplakia, erythroplakia, carcinoma in situ, and smoker's palate.

Subsites of the Oral Cavity

The American Joint Committee on Cancer (AJCC) divides the oral cavity into seven distinct subsites (mucosal lip, buccal mucosa, floor of the mouth, oral tongue, mandibular gingiva and alveolar ridge, maxillary gingiva, alveolar ridge, and hard palate, and retromolar trigone. Defining the origin subsite of OSCC has important implications on surgical management, adjuvant therapy, and survival. Floor of mouth and tongue are still the most common subsites affected by OSCC.

The boundaries of the oral cavity are defined anteriorly by the vermillion cutaneous junction of the lips, posterosuperiorly by the junction of the hard and soft palate, posteroinferiorly by the circumvallate papilla, and posterolaterally by the anterior faucial pillars.

Diagnosis of Oral Squamous Cell Carcinoma (OSCC)

Clinical Features of Oral Carcinoma

Oral squamous cell carcinoma often presents as an indurated ulcer, exophytic growth, indurated non-ulcerative patch (endophytic), or a combination of the above appearances.

Important parameters to be recorded at the primary site in clinical examination are site of the tumor; size; extension to involve adjacent structures like the skin, muscles, bone of maxilla and/or mandible, and skull base; and extensions into compartments such as the paranasal sinuses, nasal cavity, orbit, pterygoid space, masticatory compartment, and infratemporal fossa.

Physical examination includes notation of the size, location, and appearance of the primary lesion as well as clinical evidence of tumor spread to adjacent structures,

such as trismus denoting muscle involvement and paresthesias denoting neurologic involvement. Specifically related to neural spread, otalgia may indicate involvement of the ninth and tenth cranial nerves, whereas hypoesthesia of the lingual, infraorbital, and inferior alveolar nerves may denote fifth cranial nerve involvement. Palpation is used to gain an understanding of potential depth of invasion, which should be confirmed histologically given its impact on treatment decisions. The neck must always be palpated in order to assess the potential for lymph node involvement for staging and treatment planning. Regional spread to the lymph node basin in the neck needs clinical and radiologic correlation. Evaluation of distant metastasis to lungs and bones forms a part of the staging process.

Imaging in OSCC Diagnosis

A number of imaging techniques can be helpful in visualization of the complete extension of the primary tumor and of any nodal disease. MRI and/or CT with contrast are considered to be the gold standard. Computed tomography (CT) imaging is most commonly employed for this purpose, allowing imaging of the primary tumor as well as an assessment of peritumoral invasion of structures, including bone of the mandible, maxilla, and palate. In addition, CT can simultaneously assess the potential involvement of lymph node basins. Alternatively, magnetic resonance imaging (MRI) may be employed and will provide greater detail of soft tissue for lesions, such as those confined to the tongue. MRI is also superior in cases in which a large number of dental restorations are likely to create CT artifact, which will obscure the view of the primary lesion.

Where there is involvement of bone, a MRI and CT will provide better definition for resection. Marrow signal changes can only be evaluated on a MRI. The CT provides better information on cortical erosion.

Positron emission tomography (PET) continues to be studied in regard to its utility in the initial evaluation of confirmed oral cavity cancer, but to date, evidence for its superiority to the traditional techniques is limited. In addition, the higher cost of this technology is a limiting factor. The role of a PET-CT is limited. Its primary

indication is to detect an unknown primary prior to targeted biopsy. A further role for the PET-CT is in post-radiotherapy evaluation of the neck.

Ultrasound has been used for screening of nodal disease, although it is not widely considered the diagnostic modality of choice. Imaging of the chest is indicated either through standard x-ray or by CT scan if warranted.

Biopsy

Clinically suspicious lesions of the oral cavity that do not resolve spontaneously after 2 weeks require a tissue diagnosis. A tissue diagnosis is required before the formation of any definitive treatment plan. It is preferable for the treating surgeon and oncology team to evaluate the primary site and assess for regional disease.

Excisional biopsies by referring providers can make initial staging of the lesions difficult. Often if the lesions are found to be malignant, the margins maybe are inadequate and if re-excision is necessary, however the original primary site maybe very hard to locate.

Incisional or excisional biopsies remain the gold standard for histopathologic diagnosis. Biopsies can usually be done in the office setting, but general anesthesia may be necessary for lesions that are difficult to access. Accurate dimensions of the lesions should be determined before biopsies. Intraoral photographs can be helpful in documentation. It is extremely important to make sure the biopsy is of adequate depth to capture the depth of invasion of the lesion, which is essential in deciding to perform an elective neck dissection for smaller tumors as obtaining the correct depth of invasion, can affect the stage of the lesion and the need for elective neck dissection. When patients present with large lesions, it is best to take multiple biopsies, to increase the chance of obtaining a correct histologic diagnosis. It is not uncommon to see dysplasia at the margins and necrosis or inflammation at the central part of the lesion.

Older biopsies techniques have called for an inclusion of adjacent normal tissue. However, this is not necessary for lesions that are highly suspicious for carcinoma. The goals of biopsy of highly suspicious lesions are to provide a tissue diagnosis and to provide the depth of invasion if the lesion is malignant. The oral cavity is

the only subsite in the head and neck that inclusion of normal tissue has been advocated for.

Histological Features and Grading

Pathologist is expected to report on the tumor grade—well-differentiated squamous cell carcinoma, Grade 1; moderately differentiated squamous cell carcinoma, Grade 2; or poorly differentiated squamous cell carcinoma, Grade 3. Well-differentiated tumors resemble normal squamous epithelium to a large degree, poorly differentiated tumors exhibiting little or no histologic traits of the squamous phenotype, and moderately differentiated tumors having an intermediate morphology between the two ends of the spectrum. Higher grades have strong potential for recurrence and lymph node metastasis.

Several prognostic indicators have consistently demonstrated a correlation with disease-specific survival, local and regional recurrence, and lymph node metastasis in numerous single or multicenter studies. The prognosticators are depth of invasion (DOI), pattern of invasion (POI), perineural invasion (PNI), lymphovascular invasion (LVI), and extranodal extension (ENE).

❖ Depth of Invasion/Tumor Thickness

It is important to differentiate between depth of invasion and tumor thickness. The DOI is a more predictable prognosticator compared to the latter. It is known that exophytic tumors (verrucous carcinomas being the prototype) or predominantly exophytic tumors have a good prognosis, whereas endophytic or deeply infiltrating tumors are aggressive.

Depth of invasion (DOI) is an important independent factor in prognosis with strong effect on disease-free survival and overall survival, correlating with propensity for nodal spread better than tumor size in oral cancer. In the floor of the mouth, 1-cm-wide tumor infiltrating at 0.7 cm depth will likely have a worse outcome and carries a higher risk of neck metastasis than a 2-cm-wide tumor with microinvasion or superficial invasion (e.g., less than 2 mm in thickness).

❖ Pattern of Invasion

Pattern of tumor invasion is an important prognostic factor. Tumor interface abutting deeper tissues has better prognostic value as compared to multiple tumor satellites into the deeper tissues.

❖ Perineural Invasion (PNI)

PNI presence is a soft indicator for local recurrence and decreased survival. Multiple studies have shown conflicting results. However it is one of the most important predictors of neck metastasis alongside DOI. PNI increases the rate of occult metastasis.

❖ Lymphovascular Invasion (LVI)

Histopathological presence of lymphovascular invasion has poorer prognostic outcome. The presence of LVI is associated with nodal spread or occult metastases. Literature review has conflicting evidence regarding the importance of LVI.

❖ Bone Invasion

It is common to see OSCC of gingival buccal sulcus (GBS) and retromolar trigone (RMT) invade the adjoining mandible, maxilla, and pterygoid column. This upstages the tumor to a T4.

The increased risk of local recurrence can be attributed to two factors—tumor character and margin status following resection. Invasion into the pterygoid spaces makes surgical resection difficult. Close margin is expected in these advanced tumors. Mandible infiltration can be of periosteal fixation, cortical erosion, or medullary invasion. Deeper invasion has poor prognosis.

Neck Assessment in OSCC

The cervical lymphatic basins draining the head and neck contain approximately 300 lymph nodes, which make up 40% of the body's total of ~800, and are invested in a network of fibrofatty tissue. The nodes are interconnected by lymphovascular channels. Considered the most important prognostic indicator in

head and neck epithelioid carcinomas, regional lymph node metastasis decreases survival by more than 50% compared to localized disease. Therefore, the AJCC staging guidelines have long made the clinical and pathologic metastatic nodal status a critical factor in prognosis and management of the patient. However, though the presence of extranodal extension (ENE) has long been reported to be a critical factor in prognosis of the patient, it was not until the most recent edition of the AJCC (8th edition) that ENE was brought into the clinical and pathologic staging process. ENE is so significant that it now upstages all OSCCs. Radical neck dissection, first described by Crile in 1905, was once performed in conjunction with resection of nearly all primary head and neck cancers. Removal of at-risk lymph nodes may comprise an elective versus therapeutic neck dissection, i.e., lymphadenectomy in the absence or presence, respectively, of clinically or radiographically evident lymph node metastasis. In the current era, selective neck dissection with preservation of the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve is recommended prophylactically for all but the most superficial head and neck tumors.

In addition to the presence of metastatic nodes, the presence of ENE, and the location (ipsilateral, contralateral, bilateral), size, and number of metastatic node, and level have been found to be critical during the preoperative workup. Per National Comprehensive Cancer Network (NCCN) guidelines, the preoperative workup for metastatic disease includes clinical examination, and a CT of the neck with contrast. Further adjuncts include the use of PET imaging and MRI. Some now recommend MRI as the standard of care when compared to CT for evaluating the neck for metastatic disease. To assist with treatment planning, the draining nodal basins are divided into seven anatomic and radiographic levels, I-VII. The clinician should evaluate each level of the neck, systematically, with clinical examination and imaging.

OSCC tumors have relatively predictable lymphatic drainage patterns to the over 300 lymph nodes in the neck, and this has been well documented. The purpose of the defined levels of the neck is to allow clinicians to have a uniform way to communicate with each other. In addition, clinicians can plan surgical management of the neck based on where the primary is located in the oral cavity.

Level I is divided into two important lymph node groups commonly affected by OSCC. Level IA, the submental group, is defined as those contained within the boundaries of the submental triangle (bordered by the anterior belly of the digastric muscles laterally, the hyoid bone inferiorly, and the mandibular symphysis superiorly). Level IB, also called submandibular nodes, refers to the nodes that lie within the boundaries of the submandibular triangle (bordered by the anterior and posterior bellies of the digastric muscles anteriorly and inferiorly, and the body of the mandible superiorly, and stylohyoid muscle posteriorly). Given these lymph node groups lie in close proximity to the submandibular gland, it is removed to facilitate complete clearance of all lymph nodes at level IB. For primary sites such as the lip, buccal mucosa, anterior nasal cavity, or soft tissue of the cheek, perifacial lymph nodes, including buccinator nodes, that are located outside of the submandibular triangle superior to the mandibular body, may harbor metastases. The neck dissection performed should be modified to encompass the perifacial nodes.

Level II is divided into two important groups and encompasses the region surrounding the upper third of the internal jugular vein and adjacent spinal accessory nerve. This level (A and B) extends inferiorly from the level of the carotid bifurcation (surgical landmark) or inferior body of the hyoid bone (clinical landmark) inferiorly to the skull base superiorly. The lateral border is the posterior aspect of the SCM, and the medial border is the stylohyoid muscle. A perpendicular plane defined by the posterior aspect of the submandibular gland could serve as the radiologic landmark for this medial border. Level II is further divided into sublevels IIA and IIB. These divisions are separated by the spinal accessory nerve, whereas it makes the posterior border of level IIA and the medial (anterior) border of level IIB. Nodal metastases to sublevel IIB are greatest for tumors that arise in the oropharynx rather than OSCC and laryngeal cancer.

The rate of metastasis to level IIB for pure OSCC primaries has been shown to be 7%, and dissection of this level has to be weighed against morbidity to the spinal accessory nerve.

Level III often serves as the most inferior aspect of elective neck dissection for N0 OSCC. It contains the middle jugular lymph node group, which is located around the middle third of the IJV and extends superiorly from the carotid bifurcation (surgical landmark) or the inferior aspect of the body of the hyoid bone (clinical and radiologic landmark). The inferior border is the junction of the omohyoid muscle with the IJV (surgical landmark), hence the old nomenclature of supraomohyoid neck dissection (for dissection of levels I–III). The inferior clinical and radiologic landmark is a horizontal plane defined by the lower border of the cricoid cartilage. The lateral (posterior) border is the posterior aspect of the SCM (or sensory branches of the cervical plexus). The medial border is the lateral border of the sternohyoid muscle. The lateral aspect of the common carotid artery is the radiologic landmark for the medial border.

The level IV nodal group contains those around the lower third of the IJV. They extend superiorly from the omohyoid muscle (surgical landmark) or cricoid arch (clinical landmark) superiorly and inferiorly to the clavicle. The lateral border is the posterior aspect of the SCM (or sensory branches of the cervical plexus), and the medial (anterior) border is the lateral aspect of the sternohyoid muscle. The radiologic medial border is the lateral aspect of the common carotid artery. There is also a debate whether level IV should be included in a selective neck dissection for OSCC for N0 and N1 OSCC. There is a fear of skip metastases to this level, although recent reports suggest this is not common. A recent meta-analysis demonstrated very low rates of skip metastasis to level IV in patients with cN0 (clinically N0) OSCC.

Level V, or the posterior triangle group of lymph nodes, encompasses three predominant lymphatic pathways within the posterior triangle: nodes located along the spinal accessory nerve as it travels through the posterior triangle (VA), nodes located around the transverse cervical vesseles as it travels through the lower posterior triangle (VB), and supraclavicular nodes located just above the clavicle (VB). Level V is divided into level VA and level VB. The borders of level V include the anterior border of the trapezius muscle laterally (posterior), the posterior border of the SCM medially (anterior), and the clavicle inferiorly. Supraclavicular lymph nodes extend below the level of the upper horizontal border

of the clavicle to include a particular node of importance—Virchow's node (sentinel). A horizontal plane that corresponds to the inferior border of the cricoid cartilage divides level V into sublevels VA and VB. Metastases to level V are very rare for OSCC primaries. Level VA is bordered inferiorly created by the inferior border of the cricoid cartilage, superiorly by the apex made of by the convergence of the trapezius and SCM. The anterior border is made up of the posterior border of the SCM (or sensory branches of the cervical plexus). The posterior border is made up of the anterior border of the trapezius. The inferior border of level VB is the clavicles. The superior border is the horizontal plane created by the lower border of the cricoid cartilage, the anterior border is the posterior border of the SCM (sensory branches of the cervical plexus), and the posterior border is the anterior border of the trapezius.

The nodal groups most at risk of metastasis are widespread throughout the neck and are those that extend from the mandible and skull base superiorly, to the clavicle inferiorly, to the posterior triangle bilaterally, to the midline viscera of the neck. Approximately 30% of clinically node-negative patients, that is nodal metastasis undetectable on clinical or imaging examination, will demonstrate occult metastasis on elective neck dissection. The presence of regional metastatic disease in head and neck cancer ($\geq$ N1) lowers the survival of rate for head and neck cancer patient by 50%. There has been a growing body of evidence showing that depth of invasion is a predictor for occult nodal metastasis.

Sentinel Node Biopsy

A sentinel lymph node biopsy (SLNB) is a procedure in which the sentinel lymph node is identified, removed, and examined to determine whether cancer cells are present. It is used in people who have already been diagnosed with cancer. A radioactive substance and/or blue dye are injected near the tumor. The injected material is located visually and/or with a device that detects radioactivity. The sentinel node(s) (the first lymph node(s) to take up the material) is (are) removed and checked for cancer cells.

A negative SLNB result suggests that cancer has not yet spread to nearby lymph nodes or other organs.

A positive SLNB result indicates that cancer is present in the sentinel lymph node and that it may have spread to other nearby lymph nodes (called regional lymph nodes) and, possibly, other organs. This information can help a doctor determine the stage of the cancer (extent of the disease within the body) and develop an appropriate treatment plan.

Sentinel node biopsy relies on the fact that metastases to the regional lymph nodes follow a predictive pattern in most cases. Migration of cancer cells is often to the first echelon node. It is therefore predicted that if the first echelon node is negative, the more distal node is unlikely to have cancer cell migration.

Sentinel lymph node biopsy (SLNB) has long been reported as an adjunct in melanoma and breast cancer. SLNB is used in Europe and selected North American centers and is currently undergoing investigation as an alternative to selective neck dissection in the T1-2N0 oral cavity primaries. Per the 8th edition AJCC guidelines, sentinel node biopsy is an alternative to elective neck dissection for selected smaller T1–T2 tumors. The first echelon node in most oral cancers is at level I or level II.

AJCC Eighth Edition Clinical Staging System

T—Primary tumor.
Tx—Primary tumor cannot be assessed.
Tis—Carcinoma in situ.
T1—Tumor ≤ 2 cm in greatest dimension, ≤ 5 mm depth of invasion (DOI not tumor thickness).
T2—Tumor ≤ 2 cm with DOI > 5 mm or tumor > 2 cm and ≤ 4 cm with DOI ≤ 10 mm.
T3—Tumor > 2 cm and ≤ 4 cm with DOI > 10 mm or tumor > 4 cm with DOI ≤ 10 mm.
T4—Moderately advanced or very advanced local disease.
T4a—Moderately advanced local disease.

Lip: tumor invades through cortical bone or involves the inferior alveolar nerve, floor of the mouth, or skin of the face (i.e., chin or nose).

Oral cavity: tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face). **Note:** Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.

T4b—Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery.

Regional lymph nodes (N) ENE—extranodal extension.

Nx—Regional lymph nodes cannot be assessed.

N0—No regional lymph node metastasis.

N1—Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE (−).

N2—Metastasis in a single ipsilateral lymph node, > 3 cm but ≤6 cm in greatest dimension and ENE (−); *or* mets in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE *(−); or* mets in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE (−).

N2a—Metastasis in single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE (−).

N2b—Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE (−).

N2c—Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE (−).

N3—Metastasis in a lymph node >6 cm in greatest dimension and ENE *(−) or* metastasis in any lymph node(s) with clinically overt ENE (+).

N3a—Metastasis in a lymph node >6 cm in greatest dimension and ENE (−).

N3b—Metastasis in any lymph node(s) with clinically overt ENE (+).

Distant metastasis (M).

M0—No distant metastasis (no pathologic M0; use clinical M to complete stage group).

M1—Distant metastasis.

Table 81.1 AJCC prognostic staging groups according to the eighth AJCC edition

Clinical group	T	N	M
0	Tis	N0	M0
I	T1	N0	MO
II	T2	N0	MO
III	T3	N0	MO
	T1 T2 T3	N1	MO
IVA	T4a	N0	MO
	T1T2T3T4a	N1, N2	M0
IVB	T4b	Any N	MO
	Any T	N3	M0
IVC	Any T	Any N	M1