12 ■ ORAL CAVITY CANCER

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QUICK HIT ■ Unlike oropharyngeal SCC, HPV infection is not associated with oral cavity SCC (OC-SCC). Primary management of oral cavity cancers is generally surgical resection with selective neck dissection (levels IB–III, others as indicated by primary site location and stage), followed by risk-adapted postoperative RT with or without concurrent CHT. Early-stage lesions (particularly lip) may be treated with definitive RT using brachytherapy. DOI is important for decision-making in oral cavity cancers.

EPIDEMIOLOGY: Estimated incidence of 35,000 and 7,000 deaths in the United States in 2020 and comprises 30% of all H&N malignancies. Male-to-female ratio is approximately 3:2.[1] Most common sites for oral cavity cancer in the United States are lip and tongue. Incidence is markedly higher internationally (20-fold increase in South Asia).[2]

RISK FACTORS: Smoking and alcohol are primary risk factors for OC-SCC. Other risk factors include chewing tobacco, poor oral hygiene, periodontal disease, chronic irritation from ill-fitting dentures, betel nut, chronic sun exposure (for lip cancer), and immune suppression (HIV or solid organ transplant). Unlike OPC, majority of OC-SCC are negative for HPV, unless near circumvallate papillae.[3] Genetic syndromes associated with OC-SCC include Fanconi anemia and dyskeratosis congenita.[4,5]

ANATOMY: Oral cavity boundaries**:** anterior border junction of skin and vermilion border of lip; posterior border: junction of hard and soft palate; posterior–inferior border: circumvallate papillae of tongue; lateral border: anterior tonsillar pillars/buccal mucosa (Anatomic definition of oral cavity is listed in Table 12.1.). Atlases are available for neck nodal level definition.[6]

Table 12.1 Oral Cavity Anatomic Definition

Site	Key Features	Pattern of Drainage
Mucosal lip	Bordered by upper and lower lip vermillion. Upper lip innervated by infraorbital nerve (V2) and lower lip innervated by mental nerve (V3).	IA (lower lip), IB, II, III, facial lymphatics (upper lip)
Buccal mucosa	Mucosa of inner cheek and lips to attachment of mucosa of alveolar ridge and pterygomandibular raphe.	IB, II to IV
Alveolar ridges	Mucosa overlying alveolar process of maxilla (upper) and mandible (lower). Posterior margin of upper alveolar ridge is pterygopalatine arch and posterior margin of lower alveolar ridge is ascending ramus of mandible.	IB, II to IV
Retromolar trigone	Mucosa overlying ascending ramus of mandible, from posterior surface of last molar tooth to tuberosity of maxilla.	IB, II to IV
Floor of mouth	Mucosa overlying mylohyoid and hyoglossus muscles, extending from inner surface of lower alveolar ridge to dorsal surface of tongue.	IA, IB, II to IV

(*continued*)

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Table 12.1 Oral Cavity Anatomic Definition (*continued*)		
Site	**Key Features**	**Pattern of Drainage**
Hard palate	Mucosa extending from inner surface of superior alveolar ridge to posterior edge of palatine bone of maxillae.	II to IV
Oral tongue (anterior two-thirds of tongue)	Mobile portion of tongue from circumvallate papillae to dorsal surface of tongue at junction of floor of mouth. Sensation is from lingual nerve (V3), taste is from chorda tympani (CN VII), and motor function is from hypoglossal nerve (CN XII).	Three routes of drainage: Tip of tongue–submental nodes Lateral tongue–IB Medial tongue–deep cervical LN II to IV 15% drain to levels III to IV skipping II

PATHOLOGY: SCC comprises 95% of oral cavity cancers.[7] Less common histologies include minor salivary gland carcinomas, mucosal melanoma, lymphoma, and sarcoma. Basal cell carcinomas can arise from vermillion border of lip. Routine HPV testing is not recommended and p16 is not specific to HPV infection in oral cavity.

GENETICS: Mutation in p53, CDKN2A, Rb loss of function, and increased expression of EGFR are associated with worse prognosis.[4,5] Next-generation sequencing has identified subgroups of oral cavity tumors genetically distinct from other HPV-negative H&N cancers.[8]

SCREENING: There is no effective screening program routinely used in the United States. One study of 4,611 tobacco users older than 40 were screened with systematic inspection of oral mucosa, in which abnormal findings were seen in over 70% of patients, but cancer diagnosed in only 3% of patients.[9] One study in India suggested 27% relative reduction in risk of oral cancer death with screening by physical examination and identified subsets of patients with highest risks who derive the greatest absolute benefit.[10]

CLINICAL PRESENTATION: Symptoms include pain, nonhealing ulcer, bleeding, dysphagia, ill-fitting dentures, and halitosis. Advanced lesions can present with symptoms of facial numbness, difficulty with protrusion of tongue, and trismus. On examination, may present as visible or palpable mass or ulceration in oral cavity or palpable cervical lymphadenopathy.

WORKUP: H&P including visual inspection of tumor, size and location, palpation of tumor borders, cranial nerve examination, and cervical lymph node examination. Exam should include flexible nasopharyngolaryngoscopy to rule out second primary neoplasm. Dental evaluation is important to identify need for extraction and risk of osteoradionecrosis. Speech and nutrition evaluation as indicated.

Imaging: CT neck with contrast. PET/CT is challenging to interpret in oral cavity, but remains useful for nodal and distant staging. MRI if concern for perineural spread.

Biopsy: In-office biopsy is common if safe but EUA with biopsy may be required.

PROGNOSTIC FACTORS: Age, smoking, tumor location, stage (Table 12.2), and pathologic features (histologic grade, DOI, PNI, margin status, number and size of lymph nodes, extracapsular extension) have been associated with prognosis. Lymph node involvement was shown to be the most important prognostic factor for OC-SCC.[11] One study determined oral tongue to be associated with higher rate of local failure, distant metastases, and lower OS compared to other oral cavity subsites, while other studies have suggested no significant difference in prognosis.[12,13]

NATURAL HISTORY: Premalignant changes (white plaques known as "leukoplakia") are often present before development of invasive carcinoma. Risk of development of leukoplakia into invasive carcinoma is estimated to be 1% to 20% in 10 years.[14] Patients with stage I to stage II OC-SCC have been shown to have 5-year OS about 83% and patients with stage III to stage IVa disease have 5-year OS of 55%.[15,16] Compared with other H&N sites, OC-SCCs have higher rate of local recurrence after definitive therapy. Most frequent sites of distant metastasis are lung and bone.

STAGING

Table 12.2 AJCC 8th Edition (2017): Staging for Oral Cavity

T/M \ N		cN0	cN1	cN2a	cN2b	cN2c	cN3a	cN3b
T1	• ≤2 cm • DOI ≤5 mm	**I**						
T2	• ≤2 cm and DOI (5.1–10 mm) • 2.1 to 4 cm and DOI ≤10 mm	**II**	**III**		**IVA**			
T3	• >4 cm • DOI >10 mm							
T4a lip	• Invasion[1]							
T4a oral cavity	• Invasion[2]							
T4b oral cavity	• Invasion[3]	**IVB**						
M1	• Distant metastasis	**IVC**						

Notes: Invasion[1] = invasion into cortical bone or involves inferior alveolar nerve, floor of mouth, or skin of face. Invasion[2] = invasion through cortical bone or mandible/maxilla, into maxillary sinus, or skin of face. Invasion[3] = invasion into masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery.
cN1, single ipsilateral LN (≤3 cm) and –ENE; cN2a, single ipsilateral LN (3.1–6 cm) and –ENE; cN2b, multiple ipsilateral LN (≤6 cm) and –ENE; cN2c, bilateral or contralateral LN (≤6 cm) and –ENE; cN3a, LN (>6 cm) and – ENE; cN3b, clinically overt ENE.
pN1, single LN (≤3 cm) and –ENE; pN2a, single ipsilateral or contralateral LN (≤3 cm) and +ENE or single ipsilateral LN (3.1–6 cm) and –ENE; pN2b, multiple ipsilateral LN (≤6 cm) and –ENE; pN2c, bilateral or contralateral LN (≤6 cm) and –ENE; pN3a, LN (>6 cm) and –ENE; pN3b, LN (>3 cm) and +ENE or multiple LN any with +ENE or a single contralateral node with +ENE.

TREATMENT PARADIGM

Surgery: Initial surgical resection is standard of care. Randomized trials comparing upfront surgery vs. RT demonstrated significantly worse OS with RT alone.[17,18] Achieving negative surgical margins is critical, and if feasible, repeat resection of positive margin is preferred. Close surgical margin has historically been defined as within 5 mm; however, retrospective review demonstrated local recurrence–free survival was significantly higher with margins ≤2.2 mm, suggesting new definition for close margin to stratify patients for local recurrence.[19]

Early-stage OC-SCC can be resected without significant functional or cosmetic deficits, though hemiglossectomy, maxillectomy, and mandibulotomy for locally advanced disease can lead to significant speech and swallowing deficits, which can be managed with reconstruction. Standard transoral or open approaches are used, and minimally invasive surgery with transoral laser or robotic surgery has not been shown to provide relative benefit in this setting.[20]

For T1 lip, upper alveolar ridge, and hard palate cancer, lymph node dissection may be able to be omitted, as risk of metastasis is low. For T1 or T2 oral tongue cancer, elective lymph node dissection of levels I to IV is typically recommended for all tumors ≥2 mm DOI. Recent Senti-MERORL trial demonstrated oncologic equivalence of SLNB compared to LND for operable T1–T2 N0 patients.[21] Lower alveolar ridge, floor of mouth, buccal, and retromolar trigone cancers with clinically node-negative neck should undergo level I to level III lymph node dissection due to high incidence of occult nodal metastases. Patients with primary tumors near or involving midline should be managed with bilateral neck dissection.

Chemotherapy: Combined analysis of two prospective randomized trials demonstrated significant LRC, DFS, and OS benefit with addition of concurrent CHT to PORT in patients with ECE and positive margin (see Chapter 17 for details).[22] Two PRTs examining role of preoperative CHT demonstrated no improvement in OS with cisplatin and 5-FU or docetaxel, cisplatin, and 5-FU (TPF).[23,24]

Radiation

Indications: Typical indications include pT3–T4a; pN2–3; pT1–2N0–1 *and* one or more of the following: PNI, LVSI, margin <5 mm, or T2 oral cavity cancer with ≥5 mm DOI (can consider 4 mm based on Ganly data).[25] MSKCC and PMH nomograms can be used to assess potential benefits of PORT.[26,27] PORT should start 4 to 6 weeks after surgery. PORT can be omitted for pathologic N0 neck given excellent control rate.[28] For nonoperative cases, definitive chemoRT is a feasible and viable approach based on University of Chicago experience.[29]

Intraoral cone RT: Classic technique for small tumor size (<3 cm) of floor of mouth. Preserves salivary gland function and decreases risk of osteoradionecrosis. Intraoral cone RT uses 100 to 250 kVp x-rays or 6 MeV electrons. Local control rate around 85%.[30]

Brachytherapy: Interstitial implant can be used alone or in combination with EBRT for treatment of oral tongue, floor of mouth, or buccal mucosa. Isotopes used include Ir-192, Ra-226, Cs-137, Au-198, tantalum-182. For tumor thickness <1 cm, single-plane implant is adequate; otherwise, double-plane or volumetric implant is used. Surface mold brachytherapy can be used for select superficial (<1 cm depth) or recurrent superficial lesions of hard palate, lower gingiva, and floor of mouth. Impression is made of surface to be irradiated with HDR catheters inserted into predrilled holes or grooves in mold and sealed with dental plaster.[31]

Dose: See Chapter 17 for details. For T1–T2N0 lesions, interstitial LDR brachytherapy dose is 60 to 70 Gy delivered over 6 to 7 days, with minimum tumor dose rate at 30 to 60 cGy/hr. When brachytherapy is used in combination with EBRT, implant dose should be at least 40 Gy.

Toxicity: Acute complications include mucositis, loss of taste, xerostomia, thrush, dermatitis, dysphagia, odynophagia. Chronic toxicity includes xerostomia, lifelong need for fluoride prophylaxis, risk for dental caries and osteoradionecrosis.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 4 for details.[32]

■ EVIDENCE-BASED Q&A

■ Why is initial surgical resection preferred over definitive RT for initial management of OC-SCC?

Two PRTs, as well as several retrospective studies, suggest LRC and OS benefit for surgical resection compared to definitive RT.[17,18]

Robertson, Glasgow (*Clin Oncol* 1998, PMID 9704176): PRT of 35 patients with T2–4N0–2 OC-SCC and oropharynx randomized to surgery followed by PORT (60 Gy/30 fx) vs. RT alone (66 Gy/33 fx). Trial designed to recruit 350 patients, but was closed after only 35 patients due to significantly worse OS with RT alone. MFU 23 months. OS significantly better with surgery and PORT (relative death rate 0.24, $p = .001$). Duration of LC was significantly decreased with RT alone ($p = .037$). **Conclusion: Definitive RT is suboptimal for oral cavity cancer.**

Iyer, Singapore (*Cancer* 2015, PMID 25639864): PRT of 119 patients with stage III to stage IV H&N SCC randomized to surgery followed by PORT vs. concurrent CHT and RT. MFU 13 years. No significant difference in OS for entire cohort (45% vs. 35%; $p = .262$) and DSS (56% vs. 46%; $p = .637$) at 5 years for surgery vs. RT alone, respectively. For patients with OC-SCC, surgery up front significantly improved 5-year OS (68% vs. 12%; $p = .038$). **Conclusion: OS and DSS are significantly improved with surgery and PORT compared to RT alone for OC-SCC, but not for other sites of H&N.**

Is there benefit for elective neck dissection compared to neck dissection at nodal relapse?

Randomized data suggest survival benefit to up-front neck dissection compared to neck dissection at time of nodal relapse, though stage, pathologic features, and location of primary should be considered.

D'Cruz, India (*NEJM* 2015, PMID 26027881): PRT of 596 patients with lateralized T1–2 OC-SCC randomized to elective ipsilateral neck dissection vs. therapeutic neck dissection (at time of nodal relapse). MFU 39 months. At 3 years, elective neck dissection demonstrated significantly improved OS (80% vs. 67.5%; $p = .01$) and DFS (69.5% vs. 45.9%; $p < .001$) compared to therapeutic neck dissection. Overall rate of pathologic nodal positivity in clinically node-negative neck was 30%. Rates of adverse events were 6.6% and 3.6% in elective neck dissection and therapeutic neck dissection arms, respectively. **Conclusion: Ipsilateral elective neck dissection provides OS and DFS benefit in patients with early-stage, well-lateralized OC-SCC, compared to therapeutic neck dissection**. *Comment: Note that nodal positivity (including pN1) guided RT decision leading to imbalance, possibly explaining survival difference.*

At what DOI should neck dissection be performed in early-stage (cT1–2N0) oral tongue cancer?

Several retrospective studies have demonstrated DOI as a significant predictor for locoregional recurrence. DOI ≥4 to 5 mm has been suggested as threshold for neck dissection.

Huang, PMH Meta-Analysis (*Cancer* 2009, PMID: 19197973): Meta-analysis of 16 studies investigated negative predictive value of DOI from 3 to 6 mm for cT1–2N0 oral tongue cancer. Probability of lymph node positivity at time of dissection or nodal relapse after ≥2 years follow-up increased ≥5 mm DOI (Table 12.3). There was significant increase in nodal positivity between 4 and 5 mm DOI ($p = .007$). **Conclusion: DOI strongly predicts for cervical lymph node involvement. Elective neck dissection should be considered in patients with cN0 disease with DOI >4 mm.**

Table 12.3 PMH Meta-Analysis

DOI (mm)	False Negative Rate (%)
3	5.3
4	4.5
5	16.6
6	13

Ganly, MSKCC & PMH Combined Analysis (*Cancer* 2013, PMID 23184439): Combined analysis of 164 patients from MSKCC and PMH with pT1–2N0 oral tongue cancer treated with surgery alone (ipsilateral neck dissection, no PORT). MFU 66 months. Locoregional recurrence-free survival at 5 years was 79.9%. Regional recurrence was ipsilateral in 61% of cases and contralateral in 39% of cases. Regional recurrence was 5.7% for tumors with <4 mm DOI and 24% for ≥4 mm DOI. MVA demonstrated that tumor thickness ≥4 mm was significantly associated with regional recurrence free survival ($p = .02$). Patients with regional recurrence had significantly worse DSS (33% vs. 97%; $p < .0001$). **Conclusion: Neck recurrence was significantly higher with DOI ≥4 mm, with contralateral failures accounting for 40% of recurrences.**

What are indications and benefits for postoperative RT for OC-SCC?

Typical indications include pT3–T4a; pN2–3; pT1–2N0–1 and *one or more of the following: PNI, LVSI, close margin <5 mm, or T2 oral cavity cancer with ≥5 mm DOI (can consider 4 mm based on the preceding Ganly data).*[25] *These are inclusion criteria for RTOG 0920, investigating the role of postoperative RT with or without cetuximab. These features have also been identified in various retrospective studies as significantly associated with inferior LRC, increased DM, and inferior OS.*[33,34] *Many historical H&N studies included patients with OC-SCC (though lip subsite was often excluded).*[22,34–36]

What are indications and benefits for addition of CHT to postoperative RT?

The combined analysis of Bernier and Cooper (EORTC 22931 and RTOG 9501) suggests that ECE and positive margins are indications for postoperative concurrent chemoRT (see Chapter 17 for details). One recent trial at Tata Memorial in India also addressed this question.

Laskar (*ASCO* 2016, Abstract 6004): PRT of 900 patients with resectable OC-SCC who underwent surgery randomized to PORT alone (56–60 Gy in 5 fx/week; Arm A), PORT with concurrent weekly cisplatin (30 mg/m^2; Arm B), or accelerated PORT (6 fx/week; Arm C). MFU was 58 months. LRC at 5 years was 59.9% and 65.1% for Arm A vs. Arm B (p = .203) and 58.2% for Arm C (p = NS). Unplanned subset analysis demonstrated significantly improved LRC, DFS, and OS for patients with high-risk features (T3–T4, N2–3, and ECE) and for patients treated with standard fractionation RT and concurrent chemoRT compared to accelerated RT. **Conclusion: Intensification of therapy with concurrent CHT or accelerated RT did not improve outcomes in these patients with OC-SCC.** *Comment: Final manuscript is pending, and oral cavity cancer may have different biology in India than in the United States.*

Is there benefit to preoperative CHT, RT, or chemoRT prior to surgical resection in OC-SCC?

Several PRTs have investigated the role of induction CHT with cisplatin/5-FU or TPF with no improvement in OS. Retrospective evidence suggests benefit to downstaging for patients with unresectable disease.

Zhong, China (*JCO* 2013, PMID 23129742): PRT of 256 patients with stage III to IVA resectable OC-SCC randomized to 2 cycles of induction TPF (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5-FU 750 mg/m^2 on days 1–5) followed by surgery and PORT (54–66 Gy) vs. surgery followed by PORT. MFU 30 months. Clinical response rate to induction CHT was 80.6%. No significant difference in OS (HR: 0.977, p = .918) or DFS (HR: 0.974, p = .897) with induction TPF. Patients with clinical response or favorable pathologic response (≤10% viable tumor cells) had superior OS, LRC, and distant control with induction TPF. **Conclusion: There was no significant survival benefit with induction TPF.**

Licitra, Italy (*JCO* 2003, PMID 12525526): PRT of 195 patients with T2–4 (>3 cm) N0–2 resectable OC-SCC randomized to 3 cycles of cisplatin and 5-FU followed by surgery vs. surgery alone. PORT was included for positive margin, soft tissue invasion of face, >3 lymph nodes, and/or ECE. No significant difference in 5-year OS between induction CHT and surgery alone (55% vs. 55%). Fewer patients required PORT in CHT arm (33% vs. 46%). Patients who had pCR had significantly improved 10-year OS (76% vs. 41%). **Conclusion: Induction CHT does not provide survival benefit and may decrease need for PORT.**

Mohr, Germany (*Int J Oral Maxillofac Surg* 1994, PMID 7930766): PRT of 268 patients with T2–4N0–3 OC-SCC and oropharyngeal cancer randomized to preoperative chemoRT (36 Gy/18 fx with concurrent cisplatin) followed by surgery vs. surgery alone. Surgery was completed 10 to 14 days after preoperative chemoRT. Locoregional recurrence was higher with surgery alone compared to preoperative chemoRT (31% vs. 15.6%). OS for preoperative chemoRT vs. surgery alone was 19% vs. 28%, respectively. **Conclusion: Induction chemoRT may provide LRC and OS benefit compared to surgery alone.**

What are the patterns of failure after PORT?

Retrospective series have demonstrated that contralateral neck failure is common after ipsilateral neck RT and majority of failures are local, within high-dose RT field.

Chan, PMH (*Oral Oncol* 2013, PMID 23079695): RR of 180 patients treated with PORT for stage I to stage IV OC-SCC (46% oral tongue, 23% floor of mouth, 12% hard palate, 9% buccal). MFU 34 months. LC, LRC, and OS at 2 years were 87%, 78%, and 65%, respectively. Of 38 locoregional failures, 26 were in-field. Contralateral failure occurred in 3 of 12 patients treated to ipsilateral neck only and more common in patients with N2b disease. **Conclusion: Bilateral neck RT may be beneficial in patients with N2b disease.**

Yao, University of Iowa (*IJROBP* 2007, PMID 17276613): RR of 55 patients treated with IMRT for OC-SCC (49 patients received PORT, 5 received definitive RT, and 1 received preoperative RT). OS and LRC at 2 years were 68% and 85%, respectively. All failures were in high-dose RT field, except for 1 patient who failed in lower contralateral neck. Median time to LRR was 4.1 months and LRC was significantly lower in patients with ECE. **Conclusion: Most failures after PORT are in-field.**

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