CHAPTER 32

Oral Cavity

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INCIDENCE

For 2015, there were 30,260 estimated new cases and 5990 estimated deaths.

BIOLOGIC CHARACTERISTICS

The natural history of oral cavity carcinoma depends on its anatomical site, histologic type, and stage of the tumor.

STAGING EVALUATION

A physical examination should be performed to determine the location and extent of the primary tumor and to assess for presence and extent of nodal involvement.

Computed tomography (CT) scanning will help to determine the extent of the tumor (particularly, deep invasion), detect bone invasion (CT plus panoramic x-ray film [Panorex] view) and to assess regional lymph nodes; for retromolar trigone lesions, magnetic resonance imaging (MRI) is useful to assess muscle invasion; and chest radiograph to detect pulmonary metastases. The routine use of positron emission tomography (PET) is not recommended.

PRIMARY THERAPY

For early disease (T1 to early T2 lesions), single modality surgery or radiotherapy (RT) can achieve excellent local control and survival in most oral cavity sites (85% to 90%). The treatment choice is predicated on function and treatment side effects.

Moderately advanced (large T2-early T3) lesions are treated with RT alone or surgery plus irradiation with moderate local control (60% to 80%).

LOCALLY ADVANCED DISEASE

Locally advanced disease (large T3 to T4 lesions), combined RT plus surgery is indicated in most sites because single modality disease control is poor (≤30%). RT alone or combined with concomitant chemotherapy likely results in a lower probability of cure.

For locally recurrent cancers seen after the primary tumor has been treated with surgery alone, salvage with surgery is appropriate, followed by postoperative RT, RT with or without chemotherapy, or palliative RT. Reirradiation may be considered if a recurrence is low volume, unifocal, or as a result of low dose or a marginal miss. It may also be considered for a T1-T2N0 metachronous second primary that is not amenable to surgery.

Locally recurrent cancers that occur after definitive RT alone or combined with chemotherapy can be managed with surgical salvage, palliative chemotherapy, or supportive care.

PALLIATION

Moderate dose palliative RT can be given as 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1 week interfraction interval.

The estimated number of newly diagnosed oral cancers in 2015 is 30,260.[1] The estimated number of deaths is 5990.

The oral cavity consists of the lip, floor of mouth, oral tongue (the anterior two thirds of the tongue), buccal mucosa, upper and lower gingiva, hard palate, and retromolar trigone. The frequency of involvement of various locations is shown in Table 32-1.[2] After a general discussion of etiology and epidemiology, issues relative to the various subsites will be presented separately. A discussion of preradiotherapy and postradiotherapy dental care is included.

ETIOLOGY AND EPIDEMIOLOGY

Oral cavity cancer is predominately a disease of middle-aged men who use tobacco and alcohol. Approximately 95% of carcinomas appear after age 45 with an average age of 60 years.[2] The use of tobacco in any form is associated with an increased risk of oral cancer.[3-5] Some evidence suggests that patients with oral cavity cancer who continue to smoke during RT have poorer outcomes.[6] The risk of tobacco-related cancers of the upper aerodigestive tracts declines among former smokers after 5 years and after 10 years of abstention the risk may approach that of nonsmokers.[7] Although the effects of alcohol and tobacco in inducing cancers of the upper aerodigestive tract seem to be additive, the risk of alcohol consumption without tobacco use is unclear. Some studies indicate a slightly increased risk with alcohol use in the absence of tobacco, whereas others show no apparent increased risk.[8,9]

Human papillomavirus (HPV) infection, marijuana smoking, betel quid use, and drinking the beverage “mate” have also been implicated as causative agents in the formation of squamous cell carcinomas of the upper aerodigestive tract.[10-13] In recent years, oral cancers have increased among relatively young females who have never consumed alcohol or smoked. The reason for this is unclear.[14]

Smokeless tobacco (snuff) can promote carcinomas of the buccal gingival sulcus, which are diagnosed most often in older, white women living in the southeastern United States. Carcinoma of the buccal mucosa is also associated with chewing tobacco. It is commonly seen in the southeastern United States, with a male to female ratio of 3 or 4 to 1.[15] Leukoplakia is seen with oral carcinoma in approximately 15% of cases.[16]

Persons with a “Scotch-Irish” complexion (red hair and blue eyes) or prolonged exposure to sunlight are most susceptible to lip carcinoma.[17] In one series, 82% were previous or present tobacco smokers.[18] Pipe smoking is an alleged risk factor, but this has not been substantiated by most studies. Lip cancer is often associated with poor dental hygiene or edentulous patients.[18,19] Lip trauma and a history of alcohol abuse

TABLE 32-1 Distribution of Oral Cavity Cancer: 14,253 Cases

Site	Percentage
Lower lip	38
Tongue	22
Floor of mouth	17
Gingiva	6
Palate	6
Retromolar trigone	5
Upper lip	4
Buccal mucosa	2

Reprinted from Krolls SO, Hoffman S: Squamous cell carcinoma of the oral soft tissues: A statistical analysis of 14,253 cases by age, sex, and race of patients. J Am Dent Assoc 92:571, 1976.

are also related factors.[18] Most cases appear after age 40 years, but approximately 10% occur before age 40 and a few before age 30 years. This disease is uncommon in blacks.

PREVENTION AND EARLY DETECTION

This information on prevention and early detection is of major importance for patients with oral cavity cancers. It is covered in the Part B Overview, "Head and Neck Tumors," by Robert L Foote and K. Kian Ang; it will not be reiterated here.

ORAL CARE

A complete dental examination should be performed on all patients, whether dentate or edentulous, before irradiating any portion of the mandible or maxilla. The radiation oncologist should inform the patient's dentist of the anticipated RT treatment plan, including dose and location of the RT fields. To make appropriate pretherapy recommendations, the dentist should be familiar with possible post-RT complications, such as caries and osteoradionecrosis. There is a lifelong risk of impaired healing that can lead to osteoradionecrosis, especially when teeth are extracted from hypovascularized and hypocellular bone.[20] Therefore, one objective of the pretherapy oral evaluation is to determine whether teeth in the proposed irradiated area can be reasonably maintained in a healthy state for the remainder of the patient's life.

Medical, dental, and psychosocial issues that affect a person's future dental health should be assessed at the pretherapy evaluation. The patient's compliance, motivation for daily oral hygiene procedures, dental awareness, and access to dental care are predictors of dental health. A panoramic radiograph, intraoral radiographs, and hard and soft-tissue examinations should be performed to identify high-risk dental factors such as deep caries, nonrestorable teeth, root tips, bony pathology, endodontically treated teeth, periapical and pulpal pathology, and nonfunctional teeth. Teeth exhibiting periodontal disease should be evaluated to determine their long-term prognosis. Some prognostic factors for poor periodontal health include probing depths more than 6 mm, gingival recession, furcation involvement, or mobility.[21,22] Because of the numerous reported cases of progression of gingival recession and periodontal disease after RT, it may be difficult to assess the longevity of each tooth.

To reduce the future risk of osteoradionecrosis, teeth with high-risk dental factors should be removed before the patient receives doses of more than 55 Gy.[21] Whether extraction of teeth with moderate disease is indicated remains controversial. If the patient has poor resistance to dental disease or an unwillingness to perform routine dental care or fluoride applications, pretherapy extraction of moderately diseased teeth may be justified. A healing time of 14 to 21 days is recommended after extraction, before initiating of RT.[20] Extraction should be accomplished as atraumatically as possible, with alveoloplasty to remove sharp, bony projections. The dentist should coordinate dental appointments with the radiation oncologist to minimize the delay in cancer therapy. However, extraction of healthy teeth does not reduce the risk of osteradionecrosis and should be avoided.[23]

Denture adjustments, smoothing edges of sharp teeth, dental cleaning, and oral hygiene instruction can be accomplished at the pretherapy dental visit. Ill-fitting dentures that irritate mucosal surfaces should be worn with caution during RT. Daily disinfection of dental prostheses is recommended.

Impressions for custom fluoride trays can be made before or within the first 2 weeks of RT. Patients who receive RT to major salivary glands are at lifelong risk for rampant caries. Daily use of 0.4% stannous fluoride or 1.1% sodium fluoride gel for 5 minutes each evening before sleep, in custom trays, is imperative as long as natural teeth remain. Patients should be advised to refrain from rinsing, eating, or drinking for 30 minutes after fluoride application. The dentist and radiation oncologist should consistently promote proper oral hygiene and use of fluoride throughout the posttreatment years.

Clinical practice guidelines for the treatment of cancer therapy-induced oral mucositis have been published.[24] RT-induced mucositis cannot be prevented; however, excellent oral hygiene can reduce the risk of oral infections. Supersoft toothbrushes and mild toothpastes are available for patients to facilitate proper oral hygiene during and after RT.

Consultation with the radiation oncologist is required before postirradiation extraction of teeth or invasive procedures that involve the exposure of irradiated bone. Preextraction and postextraction hyperbaric oxygen therapy may be indicated to promote healing of extraction or surgical sites.

Patients should be closely monitored for possible late effects of RT to oropharyngeal regions. Trismus, xerostomia, caries, and oral candidiasis can persist or occur at any time after treatment is completed.

MOLECULAR BIOLOGY

A discussion of the molecular biology of head and neck cancers is found in the Part B Overview, "Head and Neck Tumors" preceding this chapter.

LIP CANCER

Anatomy

The lips are composed of the orbicularis oris muscle that surrounds the mouth and is covered externally by skin and internally by mucous membrane. The upper and lower lips are attached to the gingiva by raised folds of mucous membrane called the *labial frenula*. The vascular supply is from the superior and inferior labial branches of the facial arteries. The sensory nerve of the upper lip is the infraorbital nerve; the mental nerve provides sensory innervation for the lower lip.

Lymph vessels from both lips drain into the submandibular lymph nodes (level Ib). In addition, lymph from the central part of the lower lip drains into the submental lymph nodes (level Ia). The submental nodes (level Ia) drain either to the submandibular lymph nodes (level Ib) or to the jugulo-omohyoid node (level II). The submandibular lymph nodes drain to the deep cervical chain of lymph nodes (levels II to IV).[25]

Pathology and Patterns of Spread

The most common neoplasms are moderately to well differentiated squamous cell carcinomas; approximately 5% are poorly differentiated.[26] Basal cell carcinomas usually arise on the skin above or below the lip and invade the vermilion border but rarely arise from the vermilion border. Squamous cell carcinomas start on the vermilion of the lower lip and less commonly on the upper lip. The commissure is rarely the site of origin. Leukoplakia is a common problem on the lower lip and may precede carcinoma by many years.[16]

Early lesions can initially invade adjacent skin and the orbicularis oris muscle. Advanced lesions can invade the adjacent commissures of the lip and buccal mucosa, the skin and wet mucosa of the lip, the adjacent mandible, and eventually the mental nerve. The incidence of perineural invasion is approximately 2%.[27] Lymph node involvement at presentation occurs in approximately 5% to 10% of patients. An additional 5% to 10% of patients with a clinically negative neck subsequently develop lymph node metastases. The risk of lymph node involvement increases with depth of invasion, poor differentiation, larger lesions, invasion of the commissure, and recurrence after prior treatment.[19]

Hendricks et al[28] from the Mayo Clinic reported the following incidence of positive cervical lymph nodes by T stage: T1, 2%; T2, 9%; and T3, 30%. The overall incidence of adenopathy was 19% when the commissure was involved.[26] De Visscher et al[29] reported a nodal recurrence rate of 5.4% after primary surgical resection in 184 patients with squamous cell carcinoma of the lower lip. Ninety-three percent of lesions were stage I at presentation.

Clinical Manifestations and Staging

Carcinoma of the lip usually presents as a slowly enlarging exophytic lesion with an elevated border. Occasionally there is minor bleeding. Erythema of the adjacent skin may suggest dermal lymphatic invasion. Anesthesia or paresthesia of the skin indicates perineural invasion.[30]

The American Joint Committee on Cancer (AJCC) staging for lip cancer applies to lesions arising from the vermilion surface (Table 32-2).[31]

TABLE 32-2	American Joint Committee on Cancer: Oral Cavity Primary Tumor Staging
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4 (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
T4 (oral cavity)	Tumor invades through cortical bone into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b	Tumor involves masticator space, pterygoid plate, or skull base or encases internal carotid artery

Reprinted from the American Joint Committee on Cancer: Lip and oral cavity. In Edge SB, Byrd D, Compton CC, et al, editors: AJCC cancer staging handbook, ed 7, Chicago, 2010, Springer, pp 49–61.

Early lip cancers rarely require diagnostic imaging. Locally advanced, deeply infiltrating, or recurrent carcinomas may benefit from a CT scan or panoramic x-ray film to evaluate possible bony invasion and regional nodal spread.

Treatment

Early Lesions (<2 cm)

The majority of these lesions can be surgically excised with primary closure as an outpatient procedure. Surgery is satisfactory if the lip commissure does not need to be resected, and if the resulting aperture of the oral cavity permits the insertion of dentures. Postoperative RT is recommended for positive margins or perineural invasion.[27,33,34]

Tumors that should be treated with RT include those involving a commissure to obtain better cosmesis and improved local control.[35] The uncommon, poorly differentiated lesions are also preferably treated by RT to cover a more generous treatment volume and the first echelon lymph nodes. An algorithm for treatment planning is shown in Figure 32-1.

Moderately Advanced Lesions (2 cm to 4 cm)

The length of the lower lip is approximately 7 cm. Removal of more than half of the lower lip with simple closure produces a poor cosmetic and functional result so that a reconstructive procedure is usually necessary. In these cases, RT has the advantage of a better functional and cosmetic result. Traditionally, the reconstructed lip may look normal in a photograph, but it may lack sensory and motor innervation as well as elasticity. However, there have been recent improvements in the functional and cosmetic results of various reconstructive surgical procedures.[36-38]

Stranc et al[35] studied lip function in 37 patients after surgery (19 cases) or RT (18 cases) and compared them to normal controls. Compared with surgery, RT produced better preservation of lip sensation, intercommissural distance, and elasticity. Inadequate lip seal was observed in 2 of 18 patients (11%) after RT compared with 8 of 19 patients (42%) treated surgically.

Teichgraeber and Larson reviewed the M. D. Anderson Hospital experience for patients with lip cancer involving the commissure.[39] Of the 22 patients with T2 lesions who were treated with surgery, 10 patients (45%) had recurrence. There are no data for commissure involvement treated with RT, but the relative ease of RT and the cosmetic and functional results lead us to recommend RT for lesions exhibiting this pattern of spread.

Locally Advanced Lesions (>4 cm)

Large lesions are managed by resection and postoperative RT.[34] Erythema of the skin adjacent to the lesion may indicate dermal lymphatic involvement; wide-field irradiation is recommended followed by consideration of surgical resection depending on the response to RT. Management by definitive radiotherapy and concomitant chemotherapy is generally preferred in patients who are not surgical candidates.

Management of the Neck

Regional lymphatics are not electively treated for T1 and T2 lesions unless perineural invasion or commissure involvement is present. Patients with advanced (>4 cm), poorly differentiated, or recurrent tumors often require elective neck treatment. Other factors associated with an increased risk of nodal spread include perineural invasion, maximal thickness more than 6 mm, or low p27Kip1 protein expression.[40] The decision to employ elective neck irradiation or elective neck dissection depends on the modality selected for treatment of the primary tumor.

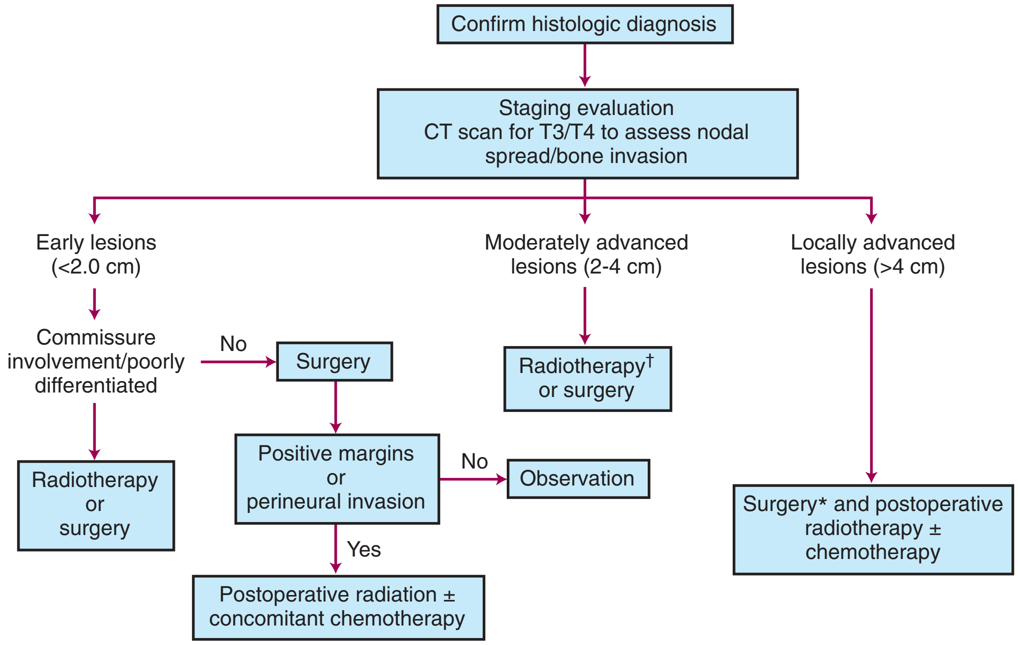


Figure 32-1 **Treatment algorithm for de novo lip cancer.** *Treat neck (neck dissection or radiotherapy).[28] †If poorly differentiated, dermal or commissure involvement.[26]

TABLE 32-3 Lip Carcinoma Treated with Interstitial Radiotherapy (*N* = 869 Patients)

Category	Local Recurrence Rate (5-year, %)	Survival Rate (5-year, %)
T1	7.4	99.5
T2	12.7	97.4
T3	26.4	81.4

Data from Jorgensen K, Elbrond O, Andersen AP: Carcinoma of the lip. A series of 869 patients. Acta Otolaryngol (Stockh) 75:312–313, 1973.

Results

T1 to T3 Lesions

Interstitial Irradiation with or without External Beam Irradiation (EBRT)

Jorgensen et al[41] reviewed 869 patients with squamous cell carcinoma who were treated with an interstitial radium implant alone; 90% of the lesions were less than 2 cm in size. The local recurrence and survival rates are shown in Table 32-3; 99% of the primary tumors were ultimately controlled with RT alone or combined with salvage surgery. Thirty-eight percent of patients with T3 tumors who developed a local recurrence developed lymph node metastases. Only 4% of patients died of lip cancer. Twenty-nine complications arose, of which two were bone necrosis.

Pierquin et al[42] reported on 50 patients with carcinoma of the lower lip treated with brachytherapy. Only one local recurrence (2%) was observed.

McKay and Sellers[26] reviewed 2854 patients; 92% of whom were initially treated with brachytherapy and EBRT. The primary lesion was controlled in 84% of the cases; 8% were salvaged later for an overall local control rate of 92%. Regional control was achieved in 58% of patients who presented with positive nodes. However, the ultimate rate of neck control was only 35% when neck nodes appeared at a later date. The cause-specific and absolute 5-year survival rates were 89% and 65%, respectively.

Tombolini et al[43] reported on 57 patients with squamous cell carcinoma of the lower lip treated with low-dose rate brachytherapy alone. Patients with clinically positive neck nodes received EBRT to the involved side of the neck. International Union Against Cancer (UICC) T stages were T1 in 27 cases (47%), T2 in 20 cases (35%), and T3 in 10 cases (18%). The 5-year local control rate was 90%.

Orrechia et al[44] treated 47 patients with T1 ($n = 21$) and T2 ($n = 26$) lip cancers with iridium-192 (^{192}Ir) brachytherapy. The 5-year and 10-year disease-free survival (DFS) rates were 92% and 85%, respectively.

Guinot et al[45] treated 39 patients with lip carcinoma using high dose rate brachytherapy twice daily to total doses ranging from 40.5 Gy to 45 Gy and observed a 3-year local control rate of 88%. Acute and chronic reactions were similar to those observed after low-dose rate brachytherapy.

Petrovich et al[46] reported on 250 patients with lip cancer treated with RT; half were treated with brachytherapy and the remainder with EBRT. Two hundred forty-seven patients (99%) had squamous cell carcinomas and 240 patients (96%) had lower lip carcinomas. The incidence of lymph node metastasis was 9%. Eleven percent experienced recurrences after RT and half were salvaged; 18 patients (7%) died of lip cancer. Moderately advanced tumors and tumors near the commissures were best treated with EBRT.

EBRT or Surgery

Babington et al[34] reported on 130 patients with lip carcinoma; 75% had T1 tumors. Initial treatment consisted of surgery (39%), RT (48%), or both (13%). Close (≤2 mm) or positive margins were observed in 27% of those treated surgically. The 2-year relapse-free survival rates were 82% and 54% after RT and surgery, respectively ($p < 0.001$). The recurrence rate after surgery was significantly higher for those with close or positive margins.

Baker and Krause[18] reported on 279 patients treated with either RT (47%) or surgery (53%) at the University of Michigan

TABLE 32-4 Carcinoma of the Lip—University of Michigan (*N* = 279 Patients)*

Extent of Primary Lesion	Patients	Local Recurrence (%)	5-Year Survival (%) Cause-Specific	Absolute
<1 cm	85	10.6	100	76
1 to 3 cm	154	9.1	92	71
>3 cm	29	20.7	71	52
Bone invasion	11	90.9	50	45

Modified from Baker SR, Krause CJ: Carcinoma of the lip. Laryngoscope 90:19–27, 1980.
**Treated by radiotherapy, 47%; treated by surgery, 53%.*

(Table 32-4). There was no difference in the 5-year cause-specific survival (CSS) rates between the two groups. Patients with positive regional nodal metastases had a 5-year CSS of 29%. Regional lymph node metastases developed in 31% of those treated for locally recurrent lesions, indicating the need for elective neck treatment for this subset of patients.

De Visscher et al[29] treated 184 patients with squamous cell carcinoma of the lower lip surgically; 93% had stage I cancers. The local and regional recurrence rates were 4.9% and 5.4%, respectively.

Mohs's Surgery

Mohs and Snow[47] reported on 1148 patients with squamous cell carcinomas of the lower lip treated with microscopically controlled surgery. The 5-year local control rates were 94.2% for those with T1 lesions and 59.6% for patients operated on for T2 lesions. The 5-year local control rates were 96.3% for well to moderately differentiated tumors compared with 66.7% for those with poorly differentiated cancers.

Holmkvist and Roenigk[48] reported on 50 consecutive patients with of squamous cell carcinoma of the lip treated with Mohs micrographic surgery (MMS). Four patients (8%) experienced a recurrence; all were successfully salvaged with additional MMS. The average time to recurrence after the initial MMS was 2.5 years. Hruza[49] also reported a relatively long interval between MMS and initial recurrence, with 20% of recurrences developing after 5 years.

T4 Lesions

Cancers that present with bone or nerve involvement are usually treated with a combination of surgery and EBRT. There are limited data pertaining to the local control rates after RT or surgery alone, ranging from 0% to 74%[26,45]; therefore, combined treatment is usually recommended. Byers et al[27] observed that 80% of patients with histologically proven perineural invasion developed cervical node metastases. Eight of 25 patients (32%) in their series who presented with either perineural invasion, tumors larger than 3 cm, or regional metastases died of disease.

The postoperative EBRT portals should include the primary site as well as the regional lymphatics (levels IA, IB, and II). The low neck is usually treated to doses sufficient for subclinical disease, and doses are frequently higher in patients with positive nodes. The total dose ranges from 60 Gy to 70 Gy, at 2.0 Gy per once-daily fraction to the primary site, depending on the pathologic findings. Higher doses with altered fractionation schemes (e.g., 74.4 Gy at 1.2 Gy per fraction twice daily), as well as concomitant chemotherapy should be considered in patients with positive margins or other high-risk factors such as extracapsular extension.[50-55]

Recurrent Lesions

Cross et al[19] reported on 563 patients treated with surgery for recurrent lip cancer. The prognosis was particularly poor for those with high-grade tumors of whom 16.7% were salvaged compared with 31.8% and 42.9% for those with well and moderately differentiated cancers, respectively. Holmkvist and Roenigk[48] reported on four patients treated with MMS; all four were salvaged.

Techniques of Irradiation

EBRT is usually delivered with either orthovoltage x-rays or electron beam. The electron beam energy depends on the tumor thickness. Lead shields are placed behind the lip to limit the dose to the oral cavity and mandible. Orthovoltage fractionation schedules range from 40 Gy to 45 Gy in 3 to 4 weeks for smaller lesions, and 50 Gy to 63 Gy in 4 to 7 weeks for moderately advanced lesions. The dose is increased 10% to 15% for electron beam RT to account for differences in the relative biological effectiveness. Orthovoltage x-rays are preferred, if available, because the maximum dose is at the surface and there is less beam constriction compared with electron beam.

An appositional field with a margin of 1 to 1.5 cm is sufficient for most small to moderately advanced lesions if orthovoltage irradiation is used. The field borders are determined by bimanual palpation. Because of beam constriction, 2.0-cm to 2.5-cm margins are necessary if an electron beam is employed. A lead shield is used to collimate the beam at the skin/lip surface.

Brachytherapy may be used as the sole treatment or in conjunction with EBRT. Implantation is usually performed under local anesthesia using ^{192}Ir sources and a single-plane plastic tube technique. The sources are arranged horizontally 10 mm to 12 mm apart with crossing sources on the lateral aspects of the implant. Three to five horizontal sources are used depending on the size of the lesion. The advantage of the plastic tube technique is that the volume of the implant is more easily adapted to the extent of the tumor and the commissure is readily included, if necessary. A gauze roll is placed between the lip and gum to increase the distance between the radioactive sources and the alveolar ridge. The recommended dose is 60 Gy to 70 Gy at a dose rate of 0.4 Gy to 0.5 Gy per hour for an implant alone. Large infiltrative lesions may be first treated with EBRT, 30 Gy at 2.5 Gy per fraction to shrink the tumor, followed by interstitial brachytherapy boost to deliver an additional 35 Gy to 40 Gy. Treatment of lip cancer with high-dose rate (HDR) interstitial needles is advocated by some.[45]

T3 and T4

Low-volume T3 cancers may be treated with primary RT, preferably combining EBRT to the primary lesion and neck followed by a brachytherapy boost. EBRT is administered with parallel-opposed fields, including the lip lesion and the level I and II lymph nodes (Figure 32-2).[56] A cork is placed in the mouth to displace the maxilla and upper lip and reduce the volume of normal tissues included in the fields. A separate anterior field is used to treat the levels III and IV lymph nodes with a tapered midline block over the larynx. The supraclavicular lymph nodes are at low risk and are not included in

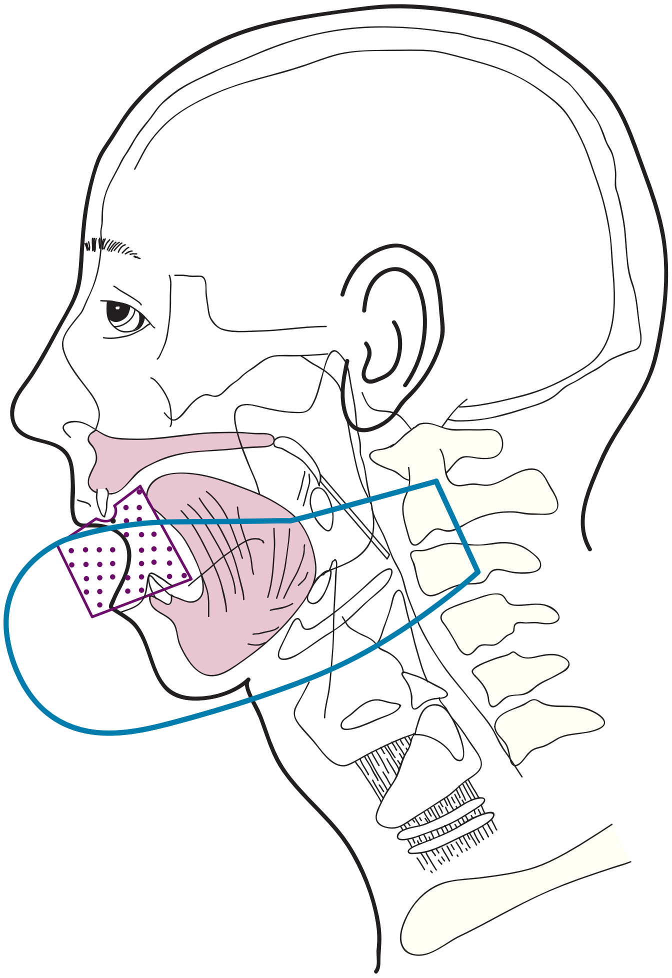


Figure 32-2 Parallel-opposed fields used to treat a carcinoma of the lower lip in conjunction with the levels I and II lymph nodes. *(From Mendenhall WM: Radiotherapy for cancer of the lip: treatment technique. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Medical Publishers Inc.)*

the fields. Both sides of the neck are treated with RT because it is unlikely that T3 and T4 primary lesions would be well lateralized.

The junction between the parallel-opposed fields and the low-neck field is at the thyroid notch. The dose fractionation schedule used varies from 38.4 Gy at 1.6 Gy twice daily to 50 Gy at 2 Gy per fraction once daily, followed by a brachytherapy boost. Low-energy photons such as 4 MV or 6 MV beams are recommended.

High-volume T3 and T4 cancers are unlikely to be cured with RT alone and are better treated with surgery and postoperative RT. RT fields are similar to those used to treat patients with RT alone. A petroleum jelly gauze bolus is placed over incisions to ensure the surface dose is adequate. The fields are extended to the skull base along the course of the third division of the fifth cranial nerve if perineural invasion is present. The dose depends on the surgical margins: negative (R0), 60 Gy; microscopically positive (R1), 66 Gy; and gross residual disease (R2), 70 Gy. Patients are treated once daily at 2 Gy per fraction, 5 days a week, in a continuous course. Intensity modulated radiotherapy (IMRT) may be employed to limit the dose to one or both parotid glands to a mean dose of ≤26 Gy to reduce long-term xerostomia if this can be done without jeopardizing target coverage.

Complications

After RT, there is gradual atrophy of the irradiated tissues. The irradiated lip must be protected from sun exposure by use of hats and ultraviolet protectants. Because the anterior teeth and gingiva are protected by lead shields when radiation is given by EBRT, radiation caries, bone exposure, and osteoradionecrosis are uncommon.

Fitzpatrick[57] reported a 3.3% incidence of late complications that required surgical intervention. Orrechia et al[44] observed a 10.6% incidence of mucosal necrosis after RT for 47 T1 and T2 lip cancers treated with ^{192}Ir brachytherapy. The risk of late complications increased with dose, dose per fraction, and volume.

FLOOR OF MOUTH

Anatomy

The floor of the mouth is a semilunar space overlying the mylohyoid and hyoglossus muscles, extending from the inner surfaces of the mandibular alveolar ridge to the ventral surface of the oral tongue. Its posterior boundary is the base of the anterior tonsillar pillar; it is bisected anteriorly by the frenulum of the tongue. The mylohyoid muscle arises from the mylohyoid ridge of the mandible and is the muscular floor of the oral cavity. The posterior insertion is at the level of the third molars.

The submandibular glands lie along the body of the mandible. The inferior aspect of the gland extends below the inferior edge of the mandibular arch; part of the gland is superficial to the mylohyoid muscle. The submandibular gland is palpable as a soft mass over the posterior portion of the mylohyoid muscle when the muscle is tensed by forcing the tip of the tongue against the maxillary incisor teeth.

The submandibular duct (Wharton's duct) is approximately 5 cm long and arises from the portion of the gland that lies between the mylohyoid and hyoglossus muscles. The duct passes deep and then superficial to the lingual nerve and exits in the anterior floor of the mouth near the midline.

The sublingual glands are the smallest of the major salivary glands and are the most deeply situated. Each lies in the floor of the mouth between the mandible and the genioglossus muscle.

The first echelon nodes for the floor of mouth are the submandibular lymph nodes (level IB), which may be stratified into preglandular, intraglandular, and postglandular groups. Lymph may also drain into the submental (level IA) nodes. These lymph nodes eventually drain to the jugulo-omohyoid (level II) nodes.[25]

The lingual nerve is a branch of the mandibular nerve and provides the sensory innervation to the floor of the mouth. It enters the mouth between the medial pterygoid muscle and the ramus of the mandible and passes anteriorly under the oral mucosa medial to the third mandibular molar.

The hypoglossal nerve (cranial nerve XII) is the motor nerve of the tongue. It passes anterior to the inferior aspect of the hyoglossus muscle and then to the lateral aspect of the genioglossus muscle. Injury to the hypoglossal nerve results in paralysis and atrophy of the ipsilateral oral tongue. The tongue deviates to the paralyzed side on protrusion because of the unopposed contralateral genioglossus muscle.

Pathology and Patterns of Spread

Most floor-of-mouth neoplasms are squamous cell carcinomas; most are moderately differentiated. Adenoid cystic and mucoepidermoid carcinomas arise from the minor salivary glands and account for 2% to 3% of floor-of-mouth tumors.

Most floor-of-mouth carcinomas are located in the anterior midline adjacent to Wharton's ducts. Extension toward the gingiva and periosteum occurs early and frequently.

Small to moderate size (stage T1 and T2) lesions are associated with metastases to the ipsilateral regional lymph nodes in 15% to 38% of cases, depending on the size and depth of invasion of the primary tumor.[58-60]

Mohit-Tabatabai et al[61] reviewed 84 patients with squamous cell carcinoma of the floor of the mouth and concluded that lesion thickness was related to the probability of subclinical cervical metastases in clinically node negative (N0) patients (Table 32-5). Patients with a primary lesion more than 1.5 mm thick had a 20% or higher risk of lymph node metastases.[61] Histologic grade and configuration of the primary lesion did not have a statistically significant correlation with subsequent development of neck node metastases. O'Brien et al analyzed the impact of tumor thickness on the incidence of regional lymph node metastases and found that the risk increased significantly for lesions 4 mm or more in thickness.[59] The reported incidence of recurrence in the untreated clinically negative neck varies from 20% to 35%.[60,62] Histologic grade and extent of vascular and perineural invasion have been implicated as predictors of lymph node spread.[63]

The distribution of clinically positive neck nodes at diagnosis is shown in Figure 32-3,[64] and the distribution of pathologically positive nodes after elective neck dissection in 62 patients with carcinoma of the floor of the mouth is shown in Figure 32-4.[65] The incidence of positive lymph nodes was 19% for those with T1 or T2 lesions and 26% for patients with T3 or T4 cancers.

TABLE 32-5 Floor-of-Mouth Carcinomas: Correlation of Primary Tumor Thickness with Neck Failure*

Thickness (mm)	T1N0	T2N0
0.1 to 1.5	1/38 (3%)	0/19
1.6 to 3.5	1/5 (20%)	3/7 (43%)
≥3.6	7/11 (64%)	2/4 (50%)

Reprinted from Mohit-Tabatabai MA, Sobel HJ, Rush BF, et al: Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. Am J Surg 152:351–353, 1986.

**Number of treatment failures/total number of patients.*

Clinical Manifestations, Patient Evaluation, and Staging

Floor-of-mouth carcinomas usually present as slightly elevated mucosal lesions with well-defined borders. A background of leukoplakia may be present. The lesions are often diagnosed by a dentist or physician during a routine physical examination.

T1 and T2 tumors may be noted initially when the patient feels a lump in the floor of the mouth with the tip of the tongue. Advanced lesions tend to produce pain, bleeding, foul breath, loose teeth, and change in speech due to fixation of the tongue.

Bimanual palpation is necessary to accurately determine the extent of induration and degree of fixation to the periosteum. Extensive lesions may exhibit invasion into the soft tissues of the neck or skin.

The AJCC staging system[32] (Table 32-2) is based on tumor size and invasion of adjacent structures such as bone or soft

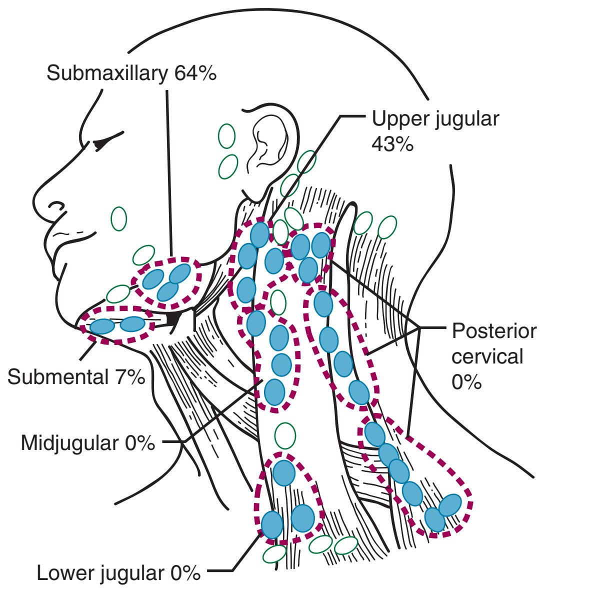
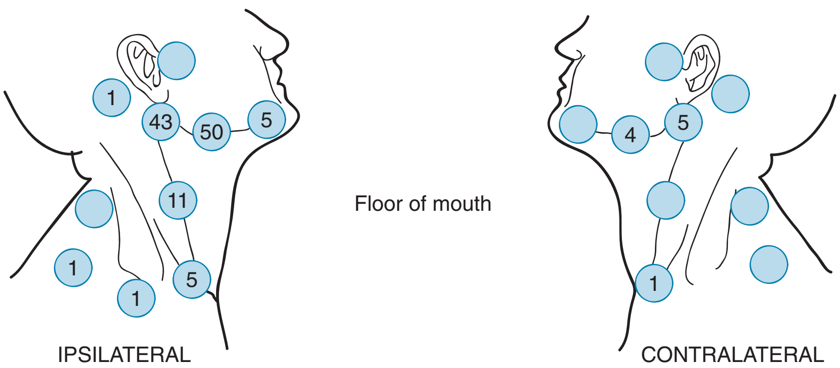


Figure 32-4 The distribution of involved neck nodes in the N0 neck when elective dissection in 62 patients with carcinoma of the floor of the mouth.
(From Byers RM, Wolf PF, Ballantyne AJ: Rationale for elective modified neck dissection. Head Neck Surg 10:162, 1988.)



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
179	38	4	17	9	11	79 / 258 = 30.5%

Figure 32-3 Carcinoma of the floor of the mouth: nodal distribution on admission, M. D. Anderson Hospital, 1948-1965.
(From Lindberg RD: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1448, 1972.)

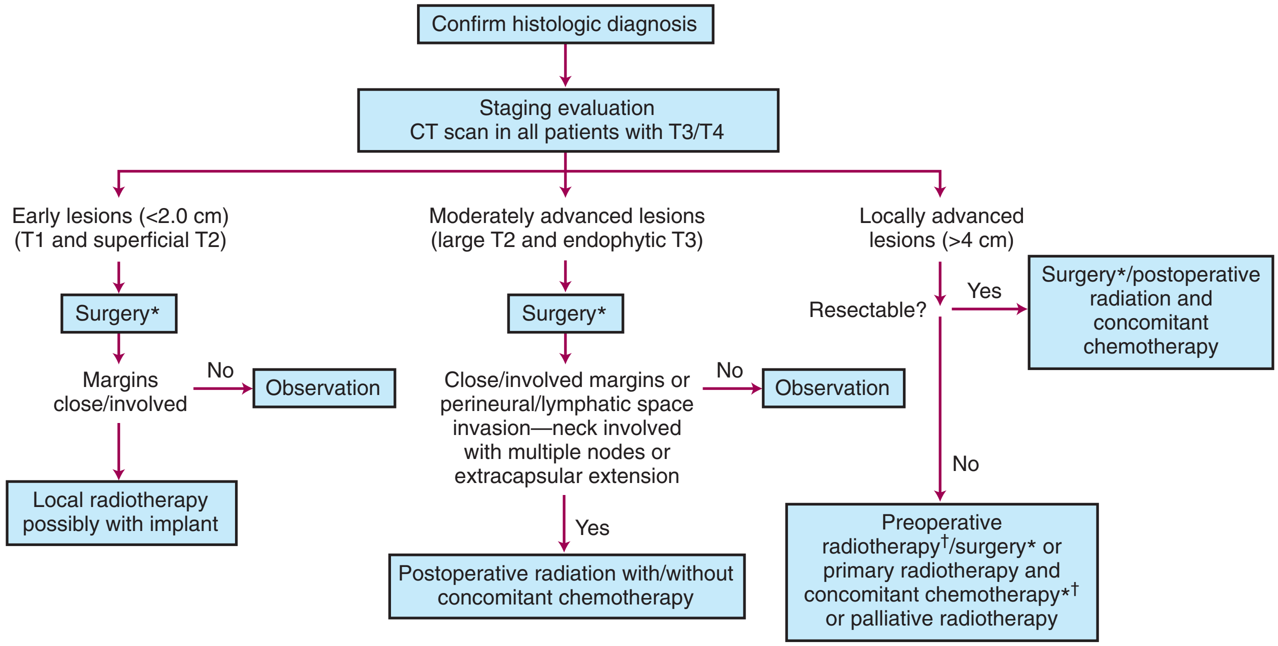


Figure 32-5 **Treatment algorithm for de novo floor of mouth cancer.** *Treat neck (neck dissection or radiotherapy) in any patient with a primary lesion >1.5 mm thick.[61] †May use concomitant chemotherapy.[72]

tissue of the neck. Radiographic studies may facilitate staging with reference to (1) the status of the mandible and teeth, (2) the deep extent of the tumor, and (3) the evaluation of the regional lymph nodes. CT scans should be obtained in essentially all patients. The mandible may be evaluated by panoramic x-ray films, dental films, and CT scanning. MRI is useful to evaluate marrow space and muscle invasion and perineural involvement.[66]

The role of PET scanning as part of the initial staging workup for oral cavity cancers has not gained widespread acceptance. It may, however, be useful in early detection of recurrences and in prediction of which patients may benefit from elective neck dissection after chemoradiation.[67-69]

Treatment

Early Lesions (T1 and Superficial T2)

Surgery and RT produce equal cure rates for T1 and superficial T2 lesions. The risk of RT induced bone and soft-tissue necrosis is significant. Therefore, surgery is usually the treatment of choice. The neck is also treated with an elective neck dissection,[70] although some advocate observation of the neck in select patients with clinically negative nodes (cN0).[71] A treatment algorithm is shown in Figure 32-5.

Sentinel lymph node biopsy is being investigated for possible use in oral cavity cancers.[73,74] However, a recent study showed that this procedure was less sensitive for floor-of-mouth cancers (80%) compared with other oral sites (100%).[75]

Some patients present after excisional biopsy of the primary tumor. If the margins are either close or involved and there is no evidence of visible or palpable residual tumor, an interstitial implant alone to the primary site is a good alternative provided that the depth of invasion is less than 1.5 mm. Reexcision may not be feasible because the surgeon does not know exactly what to remove. An additional advantage of RT is the ability to treat a larger area. Six patients were treated in this manner at M.D. Anderson Hospital[76] and seven patients at the University of Florida.[77] All had disease locally controlled and none of the patients developed regional lymph node metastases. Conversely, Sessions et al[71] have recommended reexcision rather than RT if close or positive margins are found on permanent sections.

Moderately Advanced Lesions (Large T2 and Exophytic T3 Lesions)

Infiltrative lesions with fixation or tethering to inner tables of the mandible are best treated by excision with resection of the periosteum with or without a rim of mandible. Postoperative RT is indicated for patients with close (≤5 mm) or positive margins, perineural invasion, or lymphatic space invasion.

One common indication for adjuvant RT is the inability of the surgeon to obtain adequate margins of resection, because this often leads to local recurrence,[78] even if immediate reexcision is performed.[79] Jacobs et al[80] and Laramore et al[81] reported a large intergroup study where adjuvant postoperative EBRT (60 Gy) was administered for locally advanced cancers. They found that the relapse rate was 11% in patients with satisfactory margins and 26% in those with unsatisfactory margins. Unsatisfactory margins tend to reflect a higher residual tumor burden; therefore, it may be prudent to deliver a higher dose of postoperative RT. At the University of Florida, patients with involved margins receive hyperfractionated RT to increase the dose given to the primary site while minimizing the potential late morbidity.[53] An alternative is 70 Gy in 35 fractions over 6 weeks treating once-daily, 4 days weekly and twice daily, one day per week during the last 5 weeks of irradiation.

Lapeyre et al[82] reported on 36 patients with oral tongue or floor-of-mouth carcinomas treated with brachytherapy after resection with close or positive margins. The local control was 88.5% at 2 years. Grades 2 to 3 chronic sequelae were seen in 3 of 19 patients (16%) with floor of mouth cancers.

The neck should be electively dissected if it is clinically negative. If there are multiple positive nodes or extracapsular extension, postoperative RT is indicated.[33,53] Based on the latest results of the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy

Oncology Group (RTOG) trials, concomitant chemotherapy is generally recommended as well in high-risk postoperative settings such as positive margins or extracapsular extension.[50,52]

Locally Advanced Lesions (Endophytic T3 and T4)

Patients with locally advanced floor-of-mouth cancers are treated with surgery followed by postoperative RT. In some cases, preoperative RT can be used for unresectable tumors. Patients with extensive tongue invasion with fixation or extension into the soft tissues of the neck, as well as those with massive neck disease can be treated with palliative RT (30 Gy in 10 fractions or 20 Gy in 2 fractions with a 1 week interfraction interval).

Concomitant Postoperative Chemoradiation

The issue of whether concomitant chemotherapy is beneficial when administered with postoperative RT for head and neck cancer was recently addressed by two randomized trials (RTOG 9501 and EORTC 22931).[50,52] Each of these showed an improvement in local regional control and DFS when cisplatin (100 mg/m^2) was given on days 1, 22, and 43 of the RT regimen.[50,52] Severe acute effects are seen more frequently with chemoradiation compared with postoperative RT alone.

Results

Outcomes after RT alone vary with the stage of disease and treatment technique. The RT schedules used at the University of Florida are shown in Table 32-6.[83] EBRT alone results in lower local control rates compared with brachytherapy alone or combined with EBRT.[84] The M. D. Anderson experience with RT alone is depicted in Table 32-7.[85] The failure rates range from 2% for T1 lesions to 23% and 79% for T3 and T4 lesions, respectively. For T2 and T3 lesions, brachytherapy with or without EBRT appears to result in better local control than EBRT alone.

Sessions et al[71] reported on 280 patients who were treated with surgery alone, RT alone, or combined surgery and RT. Tumor categories were: T1, 106 patients; T2, 107 patients; T3, 40 patients; and T4, 27 patients. The local recurrence rate was 41%. The 5-year CSS rates by treatment modality are shown in Table 32-8.

One hundred sixty patients with T1 (79 patients) and T2 (81 patients) floor-of-mouth cancers were treated at the Institute Gustave-Roussy with low-dose rate ^{192}Ir brachytherapy.[86] One hundred twenty-seven patients had a clinically negative neck and 33 patients (21%) had N1 neck disease. Patients with T2 and/or N1 lesions underwent a neck dissection. With a minimum follow-up of 9 years, local control rates were 93% for T1 cancers and 88% for T2 tumors.

Pernot et al[87] reported 207 patients with floor-of-mouth carcinomas treated with EBRT and ^{192}Ir brachytherapy (105 patients) or brachytherapy alone (102 patients). Tumor categories were 41%, Tl; 48%, T2; 8%, T3; 2%, T4; and 1% TX. Neck categories were 83%, N0; 12%, Nl; 3%, N2; 2%, N3. The 5-year local control rates were 97%, 72%, and 51% for Tl, T2, and T3 tumors, respectively. The 5-year CSS were: T1, 88%; T2, 47%; and T3, 36%.

Rodgers et al[88] reviewed 194 patients treated at the University of Florida. Patients with advanced lesions (T3, T4) had lower control rates when treated with RT or surgery alone compared with those treated with combined surgery and RT (Table 32-9). The 5-year CSS were: stage I, 96%; stage II, 70%; stage III, 67%; and stage IVA, 44%.

Techniques of Irradiation

Because of the proximity of the gingival ridge, which is vulnerable to high-dose RT-induced soft-tissue injury or osteoradionecrosis, the floor of the mouth has a lower RT tolerance than other portions of the oral cavity. Therefore, preirradiation and postirradiation oral care is critical.

TABLE 32-6 Carcinoma of the Floor of Mouth: RT Schedules Currently Prescribed at the University of Florida

	Interstitial Only (Gy)	Intraoral Cone Only (Gy)	EBRT ± Interstitial (Gy)	Intraoral Cone Plus EBRT (Gy)
TX—No visible or palpable tumor	55	45 over 3 wk	Not recommended	Not recommended
TX—Palpable induration or positive margins	65	55 over 4 wk	45 plus 25	15 to 18 in 10 fractions plus 50
Early superficial	60 to 65	45 over 3 wk	Not recommended	Not recommended
Early, 1 to 3 cm, induration	Not recommended	Not recommended	45 plus 25 to 30	15 to 24 in 10 fractions plus 45
Locally advanced	Not recommended	Not recommended	74.4 to 76.8 (1.2 twice a day) EBRT plus cisplatin	Not recommended

Modified from Million RR, Cassisi NJ, Clark JR: Cancer of the head and neck. In DeVita VT, Jr, Hellman S, Rosenberg SA, editors: Cancer: principles and practice of oncology, ed 3, Philadelphia, 1989, J. B. Lippincott Company, pp 488–590.
EBRT, *External beam irradiation;* TX, *status postexcisional biopsy.*

TABLE 32-7 Floor-of-Mouth Cancer: Failure to Control the Primary Lesion versus RT Technique—M. D. Anderson Hospital; January 1948 through December 1968

Category	Failure Rate (No. Failures/Total Patients)	EBRT Alone	Interstitial Alone	EBRT and Interstitial
T1	1/49 (2%)	0/10	1/31 (3%)	0/8
T2	9/77 (11.5%)	5/23 (22%)	3/34 (9%)	1/20 (5%)
T3	14/60 (23%)	9/25 (36%)	3/17 (18%)	2/18 (11%)
T4	19/24 (79%)	13/16 (81%)	2/4	4/4

Reprinted from Chu A, Fletcher GH: Incidence and causes of failures to control by irradiation the primary lesions in squamous cell carcinomas of the anterior two-thirds of the tongue and floor of mouth. Am J Roentgenol Radium Ther Nucl Med 117:502–508, 1973.
EBRT, *External beam irradiation.*

TABLE 32-8 Floor-of-Mouth Carcinoma: 5-Year Cause-Specific Survival Rates versus Treatment Modality and CTNM Stages: Washington University (N = 227)

Treatment	All Stages (N = 227)	Stage I (N = 58)	Stage II (N = 51)	Stage III (N = 54)	Stage IV (N = 64)
Local resection	76.2%	81.2%	50.0%	100%	0.0%
Composite resection	62.5%	25.0%*	100%	100%	53.9%
RT	43.2%	41.7%*	33.3%	33.3%*	53.9%
Local resection and RT	60.9%	75.0%	41.7%	100%	100%
Composite resection/RT	54.9%	94.4%	75.9%	35.0%*	40.0%
Significance level	p = 0.158	p = 0.0032	p = 0.059	p = 0.0045	p = 0.401

Reprinted from Sessions DG, Spector GJ, Lenox J, et al: Analysis of treatment results for floor-of-mouth cancer. Laryngoscope. 110(10 Pt 1):1764–1772, 2000 [table 5].
RT, *Radiotherapy.*
*Significant $p < 0.05$ by X^2/Fisher's exact test.

TABLE 32-9 Floor-of-Mouth Carcinoma: Initial and Ultimate Local Control Rates* University of Florida (N = 194 Patients)

T Category	Radiation Alone	Surgery Alone	Surgery and Radiation
T1			
Initial	32/37 (86%)	9/10 (90%)	1/1 (100%)
Ultimate	35/37 (94%)	9/10 (90%)	1/1 (100%)
T2			
Initial	25/36 (69%)	9/12 (75%)	7/7 (100%)
Ultimate	31/36 (86%)	10/12 (83%)	7/7 (100%)
T3			
Initial	11/20 (55%)	†	9/9 (100%)
Ultimate	13/20 (65%)	†	9/9 (100%)
T4			
Initial	2/5 (40%)	1/2 (50%)	5/8 (63%)
Ultimate	2/5 (40%)	1/2 (50%)	5/8 (63%)

Reprinted from Rodgers LW, Jr, Stringer SP, Mendenhall WM, et al: Management of squamous cell carcinoma of the floor of mouth. Head Neck 15:16–19, 1993 [table 2].
Grouped by initial treatment to the primary site. Forty-seven patients were excluded from local control analysis because they died within 2 years of treatment with the primary site continuously disease free.
†*No patients in category.*

T1 and T2 Cancers

Patients with superficial (≤4 mm thick), well-differentiated squamous cell carcinoma of the floor of mouth may be treated either with brachytherapy alone or, when accessible, with intraoral cone RT. Brachytherapy is not feasible if the tumor abuts or extends onto the mandibular alveolar ridge because of the risk of bone exposure. Brachytherapy may be performed with iridium using the plastic tube technique.

Intraoral cone RT is administered with either orthovoltage x-rays or electrons. Orthovoltage x-rays are preferred because there is less beam constriction and the surface dose is higher. Before each treatment, it is necessary for the radiation oncologist to verify the position of the tumor relative to the intraoral cone. Because a small volume of tissue is included in the intraoral cone field, the dose per fraction may be increased to 2.5 Gy to 3.0 Gy once daily.

Cancers thicker than 4 mm and those that are poorly differentiated have an increased risk of subclinical disease in the regional nodes. The first echelon nodes for the floor of mouth are the level I and II nodes. EBRT is delivered with either 4-MV or 6-MV x-rays using parallel-opposed fields that encompass the primary tumor as well as the first echelon nodes. An intraoral stent is placed in the mouth to displace the maxilla and upper lip out of the fields (Figure 32-6).[56] The EBRT fields are treated to 46 Gy in 23 fractions once daily or 38.4 Gy at 1.6 Gy per fraction twice daily. Brachytherapy follows the EBRT if that is the technique selected to boost the tumor. If intraoral cone RT is selected to boost the tumor, it precedes the EBRT so the extent of the tumor can be optimally defined and because it may be difficult to place the cone after EBRT because of patient discomfort. The total dose ranges from 65 Gy to 70 Gy.

The low neck (levels III and IV nodes) is irradiated with an anterior field, using 4-MV or 6-MV x-rays to 50 Gy in 25 fractions or 40.5 Gy in 15 fractions specified a D-max. The latter schedule is preferred if treatment to the upper neck will be completed in less than 25 fractions. A tapered midline block is used to shield the larynx. The junction between the parallel-opposed fields and the low neck field is at the thyroid notch (Figure 32-7).[89]

T3 and T4 Cancers

The likelihood of cure without a major complication after primary RT is low. Therefore, if patients are treated with curative intent, postoperative RT is combined with resection of the primary tumor and a neck dissection. The fields are similar to those described for patients treated with RT alone. The superior border of the field is extended to the skull base if there are multiple positive nodes or extracapsular extension. The portals are reduced off of the spinal cord at 44 Gy to 46 Gy and, if necessary, the neck posterior to the reduced fields may be irradiated with 8-MeV to 10-MeV electrons. Patients with ipsilateral positive nodes may be treated with IMRT to reduce the dose to the contralateral parotid gland and, thus, the risk of long-term xerostomia.[90,91] Patients with bilateral positive nodes are treated with parallel opposed field because parotid-sparing IMRT may result in an increased risk of a marginal recurrence. Those with negative nodes may be treated with parallel opposed fields excluding most of the parotid glands. A petroleum jelly gauze bolus is placed on the incision to ensure an adequate surface dose. Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Altered fractionation should be considered for patients with positive margins and for those with an interval of more than 6 weeks between surgery and initiation of postoperative RT. The preferred schedule at the University of Florida is 74.4 Gy at 1.2 Gy per fraction administered twice daily in a continuous course over 6.5 weeks, usually with concomitant cisplatin.

An occasional patient may present with an incompletely resectable tumor, usually because of fixed neck disease. In this event, RT precedes surgery in an effort to render the tumor

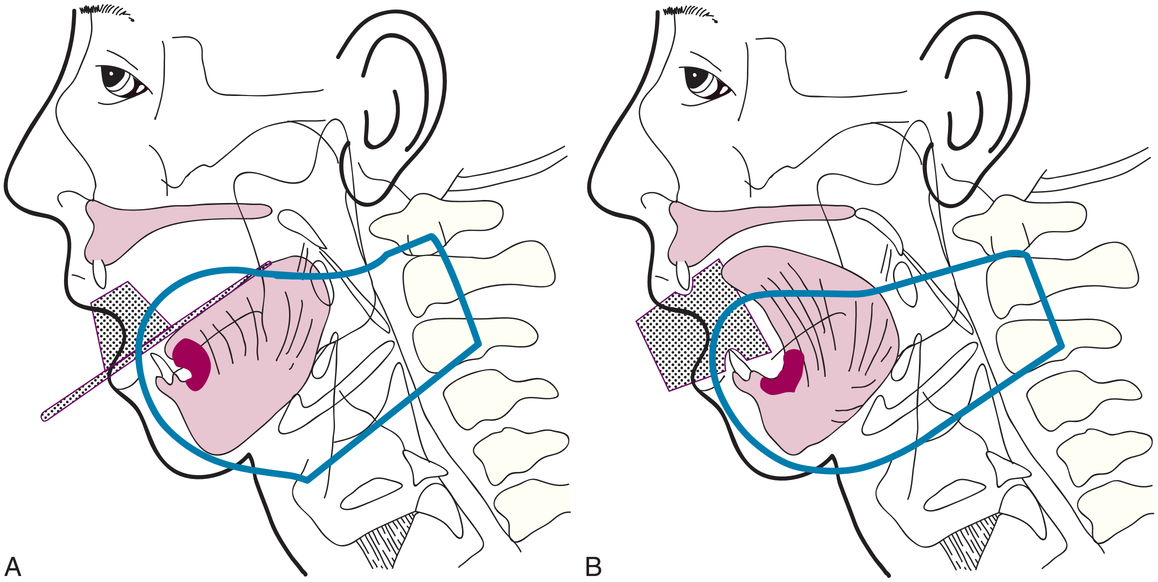


Figure 32-6 **A,** Portal for treatment of carcinoma of the floor of the mouth with tongue invasion; the tongue is depressed into the floor of the mouth with a tongue blade and cork. **B,** Portal for irradiation of limited anterior floor of mouth carcinoma without tongue invasion. Two notches are cut on a cork so it can be held in the same position between the patient's upper and lower incisors during every treatment session; the tip of the tongue is displaced from the treatment field. The anterior border of the field covers the full thickness of the mandibular arch. The lower field edge is at the thyroid cartilage, ensuring adequate coverage of the submandibular lymph nodes. The superior border is shaped so that much of the oral cavity, oropharynx, and parotid glands are out of the portal. The minimum tumor dose to the planning target volume (PTV) is specified at the primary site (i.e., not along the central axis of the portal) with the aid of computer dosimetry.
(From Parsons JT, Mendenhall WM, Moore GJ, et al: Radiotherapy of tumors of the oral cavity. In Thawley SE, Panje WR, Batsakis JG, et al, editors: Comprehensive management of head and neck tumors, ed 2, Philadelphia, 1999, W.B. Saunders Company, pp 695–719). [Figures 35-8 and 35-9, p 704].

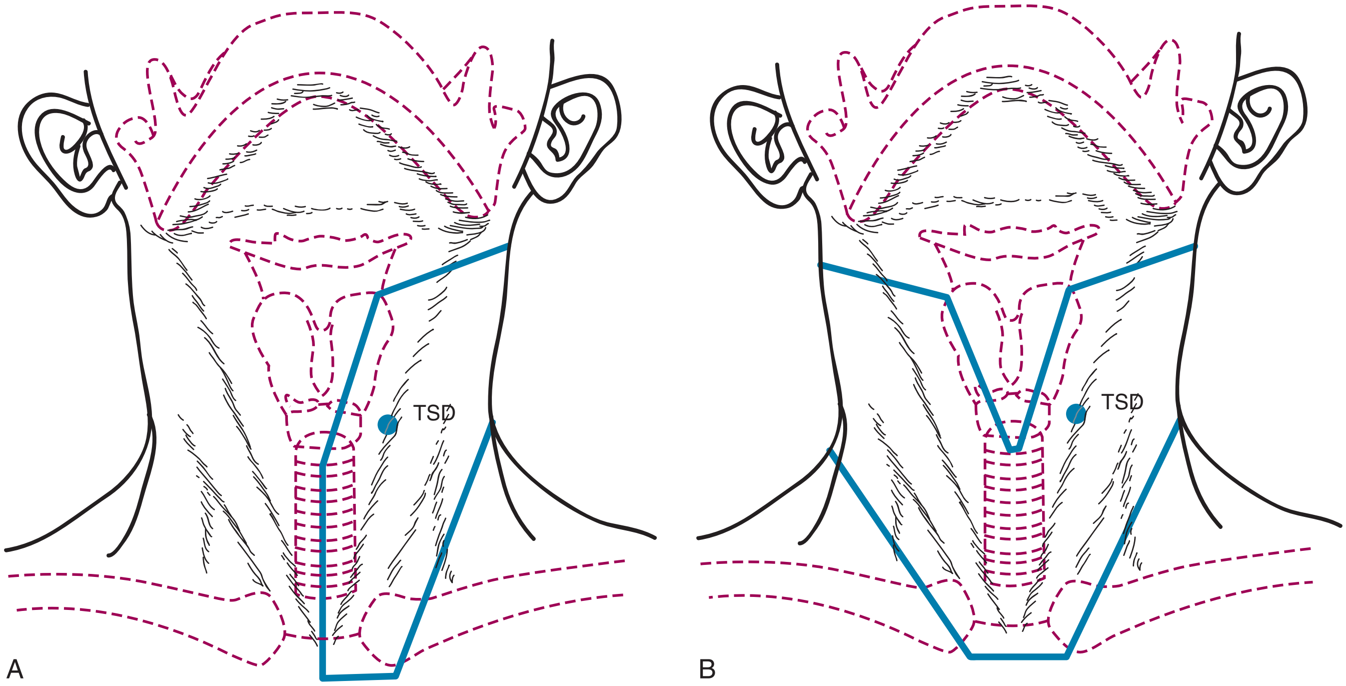


Figure 32-7 **A,** Portal used to irradiate the ipsilateral neck. In patients with N0 disease, the nodes in the lateral supraclavicular fossa are at low risk and are not irradiated electively. **B,** Fields for bilateral lower neck RT of the N0 neck. The larynx shield should be carefully designed. Because the internal jugular vein lymph nodes lie adjacent to the posterolateral margin of the thyroid cartilage, the shield cannot cover the entire cartilage without producing a low-dose area in these nodes. A common error in the treatment of the lower neck is to extend the low neck portal laterally out to the shoulders encompassing lateral supraclavicular lymph nodes that are at negligible risk while partially shielding the high-risk midjugular lymph nodes with a large rectangular laryngeal block. The inferior extent of the shield is at the cricoid cartilage or first or second tracheal ring; the shield must be tapered because the nodes tend to lie closer to the midline as the lower neck is approached.
(From Parsons JT, Mendenhall WM, Million RR: Radiotherapy of tumors of the oropharynx. In Thawley SE, Panje WR, Batsakis JG, et al, editors: Comprehensive management of head and neck tumors, ed 2, 1999, W.B. Saunders Company, pp 861–875). [Figure 10, A *is* Figure 42-2, B, p 867*]. [Figure 10,* B *is Figure 42-7,* A, *p 872].*

TABLE 32-10 Carcinoma of the Floor of the Mouth: Treatment Complications (*N* = 194 Patients)

Initial Treatment	Patients With Severe* Complications	Patients with Mild to Moderate† Complications
Radiotherapy alone	6/117 (5%)	49/117 (42%)
Surgery alone	6/36 (17%)	3/36 (8%)
Surgery and radiotherapy‡	6/41 (15%)	8/41 (20%)

Reprinted from Rodgers LW, Jr, Stringer SP, Mendenhall WM, et al: Management of squamous cell carcinoma of the floor of mouth. Head Neck 15:16–19, 1993 [table 3].
**Postoperative complications (myocardial infarction, pulmonary embolism, etc.), wound infection or dehiscence, fistula formation, or osteoradionecrosis requiring hospitalization or surgical intervention.*
†Small bone exposure, soft-tissue necrosis, or minor infection. Osteoradionecrosis or surgical wound complication requiring outpatient therapy only.
‡Preoperative or postoperative radiotherapy.

resectable. Approximately 46 Gy to 50 Gy is delivered to the primary tumor and both sides of the neck followed by a reduction and a boost to the area limiting resection to 60 Gy to 70 Gy.

Patients with advanced disease and a remote chance of cure are treated with palliative intent. The dose fractionation schedules employed at the University of Florida are 20 Gy in 2 fractions with a 1-week interfraction interval or 30 Gy in 10 fractions over 2 weeks.

Complications

A limited soft-tissue necrosis may develop in the floor of the mouth, usually at the site of the original lesion. These ulcers are painful and usually respond to local anesthetic measures (viscous lidocaine or tetracaine lollipops), antibiotics, and time. If the ulceration develops on the gingiva, the underlying mandible may be exposed. It is recommended to discontinue wearing of dentures, apply a local anesthetic and administer antibiotics. Recent data suggests that pentoxifylline, 400 mg three or four times daily, may be beneficial in this setting, and may also reduce late RT-induced fibrosis.[92] If the soft-tissue or bone necrosis progresses, hyperbaric oxygen and surgical debridement may be necessary.[93,94] Eighteen of 194 patients (9%) treated at the University of Florida developed severe complications (Table 32-10).[88]

Sessions et al[71] reported on 280 patients treated with surgery alone or RT. They observed late RT complications in 41% of patients treated by EBRT and brachytherapy, most of which appeared within 1 year of treatment. Surgical complications included infection (5%), wound slough (9.6%), orocutaneous fistula (6.1%), carotid artery exposure/blowout (1.1%), and delayed fatality (1.4%). Fifty-eight percent of these complications were related to the use of combined surgery and external RT.

Bone necrosis was seen in 18% of patients treated with brachytherapy for T1-T2 floor-of-mouth cancers at the Institut Gustave-Roussy; 2.5% were severe.[86]

ORAL TONGUE CANCERS

Anatomy

The tongue is located in the floor of the mouth, and at rest, fills most of the oral cavity. It is involved with mastication, taste, and oral cleansing; but its main functions are propelling food into the pharynx when swallowing, and forming words when speaking.

The sulcus terminalis divides the tongue into the oral and pharyngeal portions; the oral portion consists of the anterior two thirds of the tongue. The tongue is attached to the floor of the mouth by the frenulum. The circumvallate papillae are the largest taste buds; they are 1 mm to 2 mm in diameter and lie anterior to the sulcus terminalis.

The oral tongue consists of four muscles: the genioglossus, hyoglossus, styloglossus, and palatoglossus. They all originate outside the tongue and insert into it and their function is to move the tongue. There are four intrinsic muscles of the tongue that alter the shape of the tongue.

The muscles and mucous membranes of the tongue have separate nerve supplies. The hypoglossal nerve (cranial nerve XII) is the motor nerve of the tongue. It descends from the medulla and exits through the hypoglossal canal from whence it passes laterally between the internal jugular vein and internal and external carotid arteries to curve anteriorly and enter the tongue. It passes anteriorly on the inferior aspect of the hyoglossus muscle and then to the lateral aspect of the genioglossus muscle. Injury of the hypoglossal nerve results in paralysis and eventual atrophy of the ipsilateral tongue.

The lingual nerve, which is a branch of the mandibular division of cranial nerve V, is the sensory nerve for the oral tongue. For special sensation such as taste, the anterior two thirds of the tongue is supplied by the chorda tympani branch of the facial nerve (cranial nerve VII). The chorda tympani joins the lingual nerve and runs anteriorly in its sheath. The blood supply to the tongue is from the lingual artery; two lingual veins accompany the lingual artery. The deep lingual vein begins at the tip of the tongue and runs posteriorly in the median plane.

The tongue has a submucosal plexus of lymph vessels. There are three routes of lymphatic drainage from the oral tongue: the tip of the tongue drains to the submental lymph nodes (level Ia); lymph from the lateral aspects of the tongue drains to the submandibular lymph nodes (level Ib) and from there into the deep cervical lymph nodes (level II-IV); and lymph from the medial tongue drains directly to the inferior deep cervical lymph nodes (levels III and IV). Approximately 15% of patients have lymphatic metastases that bypass level II and present in levels III and IV.[95] Lymphatic drainage is unilateral; drainage to the contralateral lymphatics is unlikely.

Pathology and Patterns of Spread

Ninety-five percent of oral tongue cancers are squamous cell carcinomas. Leukoplakia is also common.[96] Verrucous carcinoma and minor salivary gland tumors occur infrequently.

Nearly all squamous cell carcinomas occur on the lateral and ventral surfaces of the tongue. Anterior-third (tip) lesions are usually diagnosed early. Middle-third lesions often invade the musculature of the tongue and subsequently extend into the lateral floor of mouth. Posterior-third lesions grow into the musculature of tongue, floor of mouth, anterior tonsillar pillar, base of tongue, glossotonsillar sulcus, and the mandible.

The distribution of clinically positive neck node metastases on presentation is shown in Figure 32-8.[64] Forty-five percent of patients with cancers of the oral tongue have clinically positive nodes at diagnosis; 5% are bilateral. Byers et al[65] reported a 19% incidence of subclinical disease for T1N0 and T2N0 lesions, and 32% for T3N0 to T4N0 cancers after elective neck dissection. Ozeki et al[97] have reported three cases with metastases to the lingual lymph nodes.

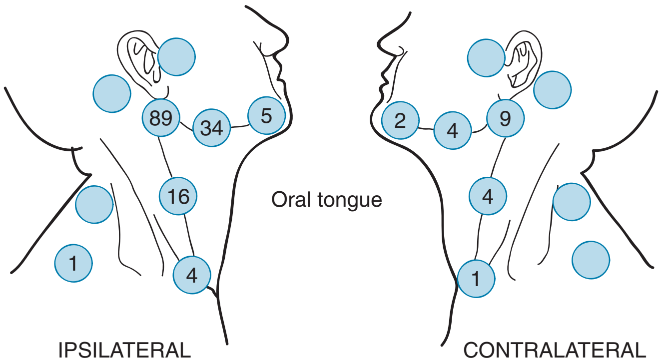
Clinical Manifestations, Patient Evaluation, and Staging

Patients with oral tongue carcinomas usually present with a sense of tongue irritation or of a mass in the tongue. Deep infiltration may affect speech and swallowing. Advanced ulcerative lesions are often associated with a foul odor and pain.

Palpation of the tongue and floor of mouth, visual examination, and assessment of tongue mobility will help define the extent of the primary tumor. CT and, to a lesser extent MRI, is useful for defining the deep extent of larger primary tumors and to assess the neck. The staging system is depicted in Table 32-2.[31]

Treatment

A treatment algorithm is shown in Figure 32-9.



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
197	40	9	32	8	16	105 / 302 = 35%

Figure 32-8 Carcinoma of the oral tongue: nodal distribution on admission, M. D. Anderson Hospital 1948 to 1965.
(From Lindberg RD: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1448, 1972.)

Early Lesions (T1 and Superficial T2)

Surgery and RT are equally effective in controlling small oral tongue cancers. Superficial well-defined lesions can be cured using resection alone with good functional results.[98,99] Postoperative RT is recommended for close or positive margins,[78,100] extensive nodal disease (large or multiple positive neck nodes), vascular space invasion, extracapsular extension, or perineural invasion.[33,53] Although the risk of a significant RT complication is low, surgery is the preferred treatment in the authors' institution because of a lower risk of bone exposure or soft-tissue necrosis that may persist for months or years after RT.

Patients are treated with definitive RT if they decline surgery or are at high risk for operative complications.[101] RT for early stage oral tongue carcinoma can be given with EBRT combined with an interstitial implant or an intraoral cone boost, or with an interstitial implant alone.[85,102] The results of EBRT alone are suboptimal.

Moderately Advanced Lesions (Large T2 and T3)

Moderately advanced primary cancers are managed by partial glossectomy followed by postoperative RT. Preoperative RT is rarely used because it is easier for the surgeon to define the extent of the tumor in the patient who is unirradiated and because the risk of postoperative complications is higher.

Advanced Lesions (T4)

The likelihood of cure for T4 tongue cancers is low. Early T4 cancer may be suitable for partial glossectomy and adjuvant RT. More advanced lesions require a total glossectomy either with or without a total laryngectomy (to prevent aspiration) and reconstruction. Preoperative RT alone or plus concurrent chemotherapy can be given to patients with unresectable tumors, giving at least 50 Gy in 25 fractions to attempt to render the tumor operable or allow the surgeon to perform a more complete resection. Patients who are in poor health or

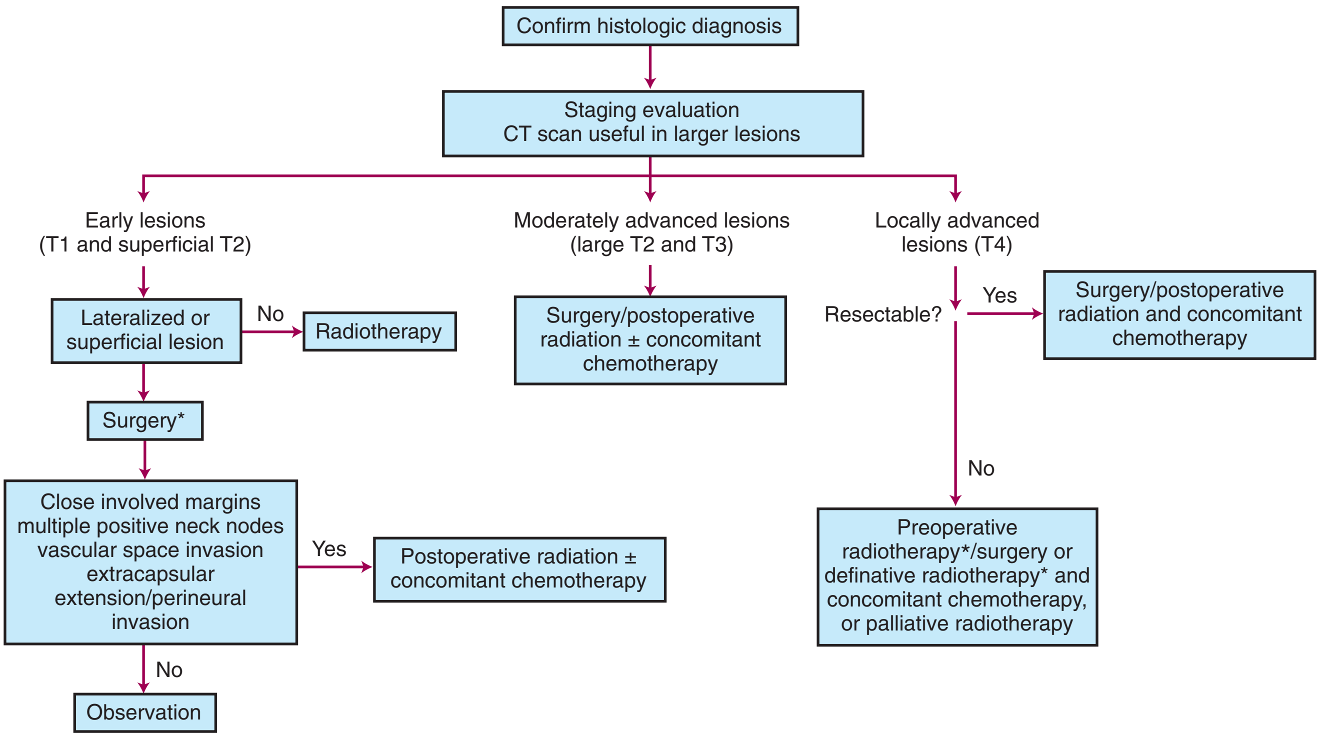


Figure 32-9 **Treatment algorithm for de novo oral tongue cancer.** *Treat neck (neck dissection or radiotherapy) for primary tumors >2 mm thick.[98]
†May use concomitant chemotherapy.[72]

who also have advanced neck disease are treated with palliative RT.

Results

Wang et al[103] evaluated results of various boost techniques combined with EBRT for patients with T1 and T2 oral tongue lesions and observed a 5-year actuarial local control rate of 54% after an interstitial implant, 50% after intraoral cone orthovoltage RT, and 86% after intraoral cone electron beam therapy. The reason that local control was better after electron beam intraoral cone boost compared with orthovoltage intraoral cone is unclear. Compared with interstitial implantation, intraoral cone RT is associated with a lower dose to the mandible and does not require anesthesia or hospitalization. It may also be associated with fewer complications. Wang et al at Massachusetts General Hospital gave 3.0 Gy per fraction for eight to nine daily fractions with intraoral electron beam RT (five fractions per week) followed immediately by EBRT with 1.6 Gy twice daily for 12 days.[103] The patient was given a 1.5 to 2 week split and resumed RT to a total EBRT dose of 51.4 Gy; the total dose is approximately 75 Gy.

Intraoral cone RT with orthovoltage x-rays is preferred at the University of Florida.[104] Patients usually receive 3.0 Gy per fraction with intraoral cone treatment for 7 to 9 days for a total of 21 Gy to 27 Gy followed by EBRT to 30 Gy in 10 once-daily fractions or 32 Gy at 1.6 per fraction twice daily over 2 weeks to the primary site and neck.

Brachytherapy may also be combined with EBRT to treat oral tongue cancer.[99,102,105] Patients treated at the University of Florida with EBRT followed by an interstitial implant had a local control rate of 83%.[101] Wendt et al[105] reported on the M. D. Anderson experience with T1N0 and T2N0 oral tongue carcinomas in which patients underwent either brachytherapy alone or combined with EBRT. Of 8 patients who were treated with EBRT alone, 5 (63%) developed a local recurrence. Six of 18 patients (33%) treated with interstitial therapy failed at the primary site. In those patients treated with a combination of EBRT and brachytherapy, the 2-year local control rate was 92% for those treated with EBRT doses less than 40 Gy combined with a moderately high brachytherapy dose, compared with 65% for patients who received EBRT doses of 40 Gy or more with a lower brachytherapy dose.[105] A review of the pertinent literature supports the efficacy of brachytherapy (Table 32-11).[84]

TABLE 32-11 Local Control of Oral Tongue Carcinoma as a Function of Radiation Modality Employed

	E + I vs E	I vs E	E + I vs I
Chu and Fletcher[85]	E + I > E	I > E	No difference
Fu et al[102]	E + I > E	I > E	E + I < I*
Horiuchi and Adachi[106]	E + I > E	I > E	E + I > I†
Lees[107]	E + I > E	I > E	No difference
Mendenhall et al[84]	—	—	E + I < I‡

Adapted from Mendenhall WM, Van Cise WS, Bova FJ, et al: Analysis of time-dose factors in squamous cell carcinoma of the oral tongue and floor of mouth treated with radiation therapy alone. Int J Radiat Oncol Biol Phys 7:1005–1011, 1981.

E, *External beam irradiation;* I, *interstitial irradiation.*

External beam plus more than 40 Gy radium produced significantly better results than external beam plus less than 40 Gy radium.

Local control alone not reported by T stage.

†*Difference noted primarily in T3 and T4 lesions.*

‡*T2 lesions.*

Subclinical disease in the neck nodes is common in patients with oral tongue cancer. Matsuura et al stressed the importance of elective treatment to the neck, especially as tumor thickness increases.[108] In their experience, patients with tumor thickness 8 mm or more were at an increased risk of nodal failure in the clinically negative neck. Wendt et al[105] also showed the importance of elective therapy to the clinically negative neck. Failure in the neck occurred in 44% of patients receiving no elective neck RT; 27% of the failures were in patients receiving less than 40 Gy compared to an 11% failure rate for those who received 40 Gy or more. Byers et al[109] recommended elective treatment to the clinically negative neck in patients with T2 to T4 primary tumors. Haddadin et al[110] observed that patients with T2 tongue carcinomas had a significantly better outcome after an elective neck dissection compared with those who were followed with salvage reserved until development of a regional failure (75% versus 39% 5-year survival rates, respectively). Based on a review of the Memorial Sloan-Kettering Cancer Center (MSKCC) experience, Spiro et al[98] recommended that elective neck therapy be given for primary tumors exceeding 2 mm in thickness because the risk of cervical metastasis approached 40% in this cohort of patients. O-Charoenrat et al[111] found that increasing tumor thickness predicted for occult cervical node metastasis and poor outcomes in patients with stages I and II oral tongue squamous cell carcinoma treated at the Royal Marsden Hospital. Univariate analysis of DFS showed poorer outcomes for patients older than 60 years ($p = 0.0423$) and with tumors thicker than 5 mm ($p = 0.0067$). The impact of tumor thickness on outcome ($p = 0.005$) was also appreciated in a multivariate analysis. They recommended elective neck treatment for tumors more than 5 mm thick.

The use of sentinel lymph node biopsy and PET scanning may alter the treatment paradigm as more experience is gained in their use for oral cavity cancers.[112]

Bourgier et al reported on 279 patients treated with exclusive low-dose rate brachytherapy with or without an elective neck dissection for T2N0 squamous cell carcinoma of the oral tongue.[113] The incidence of subclinical cervical node metastases was 45%. The 2-year local and regional control rates were 79% and 76%, respectively. The incidence of grade 3 complications was 3%.

Fein et al[101] compared the results and complications of treatment with RT or surgery for squamous cell carcinoma of the oral tongue. The control rates for RT alone or surgery alone or in combination with RT were the same for stage T1 and T2 lesions; combined modality treatment resulted in higher cure rates for T3 and T4 tumors (Table 32-12). In an analysis of patients with T1 and T2 lesions, those receiving less than 30 Gy of EBRT plus an interstitial implant had a better outcome than those receiving surgery plus or minus postoperative RT.[101] Currently, for patients receiving RT alone, a dose of 1.6 Gy per fraction is given twice daily to 32 Gy followed immediately by an interstitial implant for an additional 35 Gy to 40 Gy. This technique decreases the overall treatment time and avoids the large dose per fraction associated with 30 Gy in 10 fractions over 2 weeks.[101]

Chao et al[100] reported on 55 patients with stage T1 and T2 lesions treated with surgery and postoperative RT. Thirty-nine patients received EBRT alone and 16 patients had an interstitial implant as part of the treatment. By adding an interstitial implant for patients with positive margins, the local control was equivalent to that observed for patients with negative margins treated with EBRT alone.

Sessions et al[99] reported on 332 patients with oral tongue cancer treated with surgery or RT at Washington University. Tumor stages at presentation were T1 116 patients; T2, 128 patients; T3, 71 patients; and T4, 17 patients. Local recurrences occurred in 34% and 31% suffered a neck recurrence. The 5-year CSS versus treatment group for 279 of the 332 patients are shown in Table 32-13.

Techniques of Irradiation

T1 and T2 Cancers

Reduction of overall treatment time is vital to the successful treatment of oral tongue carcinomas with RT alone. Patients with well-differentiated carcinomas that are 4 mm or less are optimally treated with brachytherapy alone. Interstitial implantation may be accomplished with iridium using the plastic tube technique. The total dose varies from 65 Gy to 70 Gy over 5 to 7 days.

Although intraoral cone RT has been used successfully to treat oral tongue cancers, it is often difficult to immobilize the lesion so that setup reproducibility may be problematic. If treatment with an intraoral cone is chosen, then the cone is positioned so that the tumor is treated with a 1-cm margin. The intraoral cone therapy should be done before EBRT because of better tolerance and because the lesion can be clearly defined. Orthovoltage x-rays or electron beam may be used. If electrons are used, a beam spoiler or bolus is necessary to ensure an adequate surface dose. Additionally, a larger margin is necessary because of beam constriction compared with orthovoltage RT.

Patients who have poorly differentiated carcinomas, as well as those with 5 mm or more depth of invasion, should be treated with a combination of EBRT and brachytherapy. Parallel-opposed fields include the primary tumor as well as the levels I and II lymph nodes. A cork-and-tongue block displaces the tongue inferiorly and the maxilla superiorly to minimize the amount of normal tissue included in the treatment volume (Figure 32-10). The fields are weighted 3:2 to the side of the tumor and either 30 Gy in 10 fractions once daily or 32 to 38.4 Gy at 1.6 Gy per fraction twice daily is delivered over 2 to 2.5 weeks with 4-MV or 6-MV x-rays. Although ^{60}Co is an ideal beam for treatment of patients with oral cavity

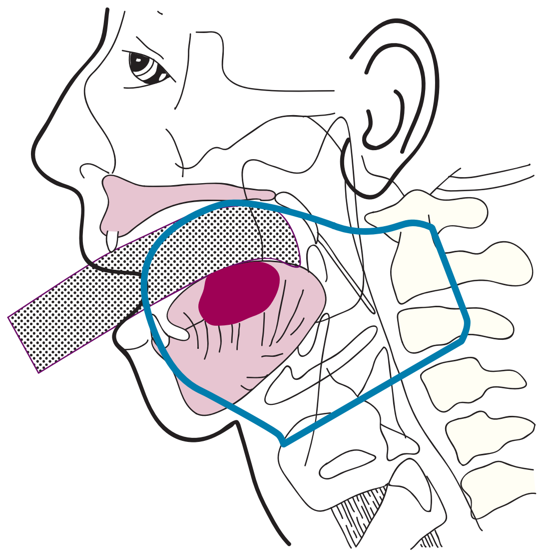


Figure 32-10 Well lateralized squamous cell carcinoma of the oral tongue (neck stage N0). A single ipsilateral field is used. The field encompasses the submaxillary (level Ib) and subdigastric (level II) lymph nodes; the entire width of the vertebral body is included to ensure adequate posterior coverage of the subdigastric lymph nodes (level II). Stainless steel pins are usually inserted into the anterior most and posterior most aspects of the lesion to the aid in localizing the cancer on the treatment planning (simulation) roentgenogram or CT scan and to confirm coverage by the interstitial implant. For lesions smaller than 2.0 cm in diameter, the low neck is not irradiated (unless the histology is poorly differentiated squamous cell carcinoma). The larynx is excluded from the radiation field. The anterior submental skin and subcutaneous tissues are shielded, when possible, to reduce submental edema and late development of fibrosis. The upper border is shaped to exclude most of the parotid gland. An intraoral lead block (stippled area) shields the contralateral mucosa. The block is coated with beeswax to prevent a high-dose effect on the adjacent mucosa resulting from scattered low-energy electrons from the metal surface. The usual preinterstitial tumor dose is 32 Gy using 1.6 Gy per fraction, twice-a-day fractionation. For larger lesions, which extend near the midline, treatment is applied by means of parallel opposed portals with no intraoral lead block.
(From Parsons JT, Mendenhall WM, Million RR: Radiotherapy of tumors of the oral cavity. In Thawley SE, Panje WR, Batsakis JG, et al, editor: Comprehensive management of head and neck tumors, vol 1, ed 2, Philadelphia, 1999, W. B. Saunders Company, pp 695–719. Copyright 1999, with permission from Elsevier). [Figures 35-17, A, B, *p 714].*

TABLE 32-12 Oral Tongue Carcinoma: Probability of Local Control at 2 Years According to T Category and Treatment Method at the University of Florida

T Category	Local Control Percent (No. Patients): Radiation Alone*	Surgery Alone or Plus Radiation	*p* Value
T1	79% (18)	76% (17)	0.76
T2	72% (48)	76% (19)	0.86
T3	45% (29)	82% (24)	0.03
T4	0% (10)	67% (5)	0.08

Adapted from Reprinted from Fein DA, Mendenhall WM, Parsons JT, et al: Carcinoma of the oral tongue: A comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck 16(4):358–365, 1994 [table 1, page 360].
Note: Numbers in parentheses indicate number of patients in each subset.
**Radiation alone or followed by a neck dissection.*

TABLE 32-13 Oral Tongue Carcinoma: 5-Year Cause-Specific Survival versus Treatment and Stage Grouping ($N = 279$)

Treatment	All Stages ($N = 279$)	Stage I ($N = 95$)	Stage II ($N = 85$)	Stage III ($N = 65$)	Stage IV ($N = 34$)
Local resection	73%*	71.4%	86.7%	33.3%	—
Composite resection	60.9%	100%	62.5%	57.1%	40%
Radiation	46%	75%	58.8%	25.0%	11.1%
Local resection and radiation	65.4%	81.0%	50.0%	71.4%	—
Composite resection and radiation	43.8%	100%	66.7%	33.3%	30.0%
Significance level	$p = 0.002$	$p = 0.770$	$p = 0.230$	$p = 0.225$	$p = 0.559$

Reprinted from Sessions DG, Spector GJ, Lenox J, et al: Analysis of treatment results for oral tongue cancer. Laryngoscope 112(4):616–625, 2002 [table 7].
**Significant at $p < 0.05$ by chi-squared/Fisher's exact test.*

cancers, it is not available in most clinics. The levels III and IV nodes are included in an anterior field as previously described. After EBRT, 35 Gy to 40 Gy is added with an interstitial implant.

T3 and T4 Cancers

Patients with T3 and T4 oral tongue carcinomas are difficult to cure with RT alone. The ability to adequately encompass the primary tumor with an interstitial implant is difficult for all but the occasional patient with a favorable low volume T3 cancer. The risk of a major complication, such as a soft-tissue necrosis or bone necrosis, is high after successful RT. Therefore, most patients are treated with surgery and postoperative RT. As for other sites, dose depends on margin status: Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Altered fractionation should be considered for patients with positive margins or for those with multiple risk factors or an interval of more than 6 weeks between surgery and initiation of postoperative RT. At our institution, the preferred schedule is 74.4 Gy at 1.2 Gy per fraction administered twice daily in a continuous course over 6.5 weeks. Concomitant cisplatin is also recommended for high-risk situations (close or positive margins or extracapsular nodal extension).[53]

Radiotherapy portals are designed to include the primary tumor and both sides of the neck (levels I to IV). The initial fields extend to the skull base to include the retropharyngeal nodes if the cervical nodes are involved. A petroleum jelly gauze bolus is placed on the incisions to ensure an adequate surface dose. IMRT may be employed to spare the contralateral parotid gland unless bilateral positive nodes are present.

Patients with incompletely resected T3 and T4 carcinomas have a poor prognosis and are treated with EBRT from 74.4 Gy to 76.8 Gy at 1.2 Gy per fraction twice daily over 6.5 weeks with concomitant chemotherapy. Thereafter, patients are evaluated for resection of residual primary tumor (nidusectomy) versus an interstitial implant. Nidusectomy is preferred because of the high risk of necrosis associated with the addition of brachytherapy. Patients who have advanced, unfavorable oral tongue cancers and who are unsuitable for aggressive treatment are treated with palliative RT consisting of either 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1-week interfraction interval.

Complications

After RT, patients may complain of a sensitive tongue, even after the mucosa appears to have healed. Taste tends to reappear from 1 to 3 months after treatment; however, because of xerostomia, post-RT taste perception is less sensitive.

Small, self-limited soft-tissue necroses are fairly common. If these occur, recurrent cancer must be ruled out. If the lesion is thought to be necrotic, conservative treatment is instituted. The patient is examined frequently and broad-spectrum antibiotics such as tetracycline are initiated as well as pentoxifylline.[92] Viscous lidocaine or a tetracaine lollipop can be applied to the ulcer for local analgesia. Hyperbaric oxygen treatment is indicated for larger progressive necroses that do not respond to conservative management. Surgery is employed as a last resort for large persistent necroses that are often associated with bone necrosis.

Osteoradionecrosis occurs infrequently; the onset varies from one month to many years after RT.[114] It is more common in patients receiving higher doses per fraction or with tumor invading the bone.[115] If a patient has dentures, the dentures must be removed or altered by the dentist to avoid trauma to areas of exposed bone; healing may require many months. Management is similar to that for soft-tissue necroses.

TABLE 32-14 Oral Tongue Carcinoma: Severe Complications (N = 170 Patients)

T Category	Radiation Alone*	Surgery Alone or with Radiation	*p* Value
T1	1/18 (6%)	1/17 (6%)	0.74
T2	6/48 (13%)	3/19 (16%)	0.50
T3	1/29 (3%)	7/24 (29%)	0.01
T4	1/10 (10%)	2/5 (40%)	0.24
Overall	9/105 (9%)	13/65 (20%)	0.03

Reprinted from Fein DA, Mendenhall WM, Parsons JT, et al: Carcinoma of the oral tongue: A comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck 16(4):358–365, 1994 [table 6, page 363].
**Radiation alone or followed by planned neck dissection.*

RT-induced xerostomia is common and is related to the volume of salivary tissue irradiated and the radiation dose. Patients who are treated with brachytherapy or intraoral cone RT without EBRT usually retain salivary function.

Oral pilocarpine has been advocated by some for xerostomia. Pilocarpine exercises a broad spectrum of pharmacologic effects, including increasing the secretions of exocrine glands, most notably the salivary glands. In a multicenter, randomized, double-blind, placebo-controlled trial published in 1993, pilocarpine produced a clinically significant benefit.[116] However, its efficacy has been questioned by the outcomes of recent randomized trials.[117,118] The recommended dose is 5 mg, three to four times a day. The time interval necessary to achieve optimal results is 8 to 12 weeks.

Amifostine has been used more recently in an effort to lessen the untoward effects of RT. It can be administered either intravenously or subcutaneously.[119,120] The latter is generally felt to be more convenient and associated with less toxicity.[121] A full course of treatment with amifostine is quite expensive. This fact, coupled with its potential to cause nausea and skin reactions, has limited its acceptance in some centers.

At the University of Florida, the severe complication rate for 170 patients treated with surgery alone or in combination with RT for oral tongue cancer was compared with the severe complication rate for patients treated with RT alone; the findings are presented in Table 32-14.[101]

Sessions et al[99] reported major treatment complications in 21 of 270 patients (12.8%), most of which occurred in those receiving composite resection and RT. Complications associated with RT included orocutaneous fistula (6/224 [2.7%]), flap necrosis (1/224 [0.4%]), carotid hemorrhage (1/224 [0.4%]), xerostomia (7/224 [3.1%]), trismus (5/224 [2.2%]), radiation caries (3.1%), soft-tissue ulcer (22/224 [9.8%]), bone necrosis (14/224 [6.2%]), and dysphagia (3/224 [1.3%]).[99]

BUCCAL MUCOSA

Anatomy

The lateral walls of the oral cavity are formed by the cheeks. The buccal mucosa is composed of the inner lining of the cheeks. It is contiguous with the lips and has the same structure.

The muscle of the cheek is the buccinator. The buccal fat pad is superficial to the fascia covering the buccinator muscle and gives the cheeks a rounded contour.

Branches of the maxillary and mandibular nerves (cranial nerves V2 and V3) provide sensory innervation to the skin, cheek, and the mucous membranes lining the cheeks. The

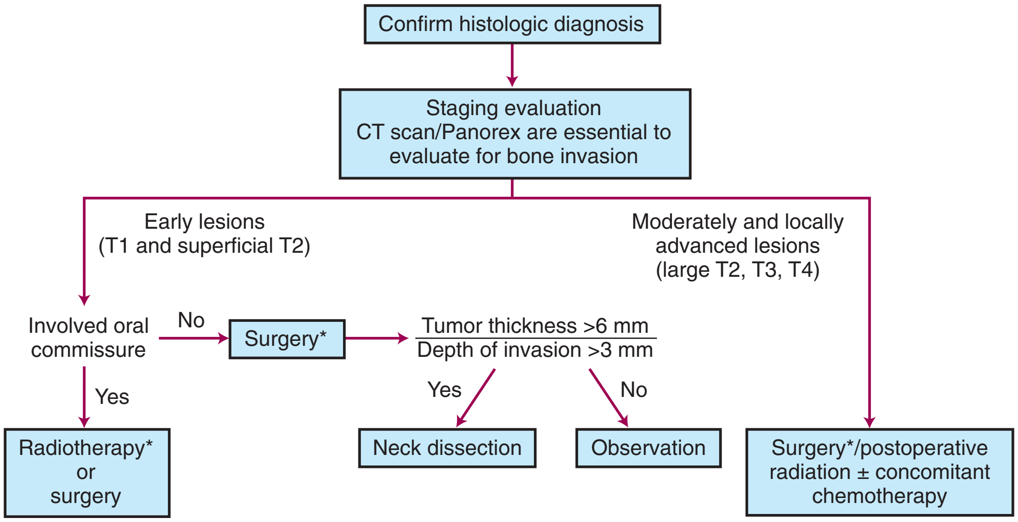


Figure 32-11 Treatment algorithm for de novo buccal mucosa cancer. *Treat neck (radiotherapy or neck dissection) for T2 to T4 tumors.[122,123]

facial nerve (cranial nerve VII) provides motor innervation to the muscles of the cheeks and lips. The lips and cheeks function together as an oral sphincter propelling food into the oral cavity. If the facial nerve is paralyzed, food tends to accumulate within the cheek along the affected side so that saliva and food dribble out of the corner of the mouth.

Pathology and Patterns of Spread

The majority of tumors originating from the buccal mucosa are low-grade squamous cell carcinomas that are frequently associated with leukoplakia. Verrucous carcinomas are observed more frequently in the buccal mucosa than in other parts of the oral cavity.[122]

Early lesions tend to be discrete, exophytic, mucosal growths. Advanced tumors tend to be ulcerated and are often associated with muscle invasion. Lesions that involve the lower gum may invade the mandible. Advanced lesions may extend to the soft tissues of the cheek.

The first echelon lymphatics are the submandibular (level Ib) and subdigastric (level II) lymph nodes. The incidence of positive nodes at diagnosis ranges from 9% to 31%; the risk of subclinical disease is 16%.[123] Bilateral cervical node metastases are unusual. Advanced cancers have a higher propensity (60%) for lymph node metastases.[122]

Clinical Manifestations and Staging

Although pain tends to be minimal, even when the lesion is large, posterior extension may result in involvement of the lingual or dental nerves which may cause ear pain. Extension behind the pterygomandibular raphe into the pterygoid muscles or into the buccinator and masseter muscles may cause trismus. Intermittent bleeding may occur when the lesions are irritated by chewing.

CT imaging can be used to evaluate the deep extension of the lesion, to detect bone invasion, and to assess the parotid and facial nodes.[66] The AJCC staging system is depicted in Table 32-2.[31]

Treatment

Early Lesions (T1 and Superficial T2 Lesions)

The preferred treatment for patients with carcinoma of the buccal mucosa is surgery. RT alone is used to treat patients by default in the uncommon situation where surgery is not feasible. Patients with T1 and T2 cancers may be treated with a combination of EBRT and an interstitial implant.[122] A treatment algorithm is shown in Figure 32-11.

Moderate to Locally Advanced Cancers (Large T2, T3, and T4)

Superficial T2 and T3 cancers may be treated with RT; however, if there is deep muscle invasion, the cure rates after RT are poor.[124,125] The preferred treatment for patients with large T3 and T4 cancers is resection of the primary tumor in conjunction with a neck dissection followed by postoperative RT. Patients who are not surgical candidates are treated with EBRT and concomitant chemotherapy. Although it would be desirable to include brachytherapy as part of the treatment, the likelihood of adequately encompassing an advanced tumor with an interstitial implant is remote, and so these patients are treated with EBRT to 76.8 Gy in 64 twice-daily fractions over 6.5 weeks. The concurrent chemotherapy regimen that is used most often at our institution is once-weekly cisplatin, 30 mg/m^2.

The management of verrucous carcinomas is controversial because of the perceived risk that the tumor may become more aggressive if it recurs after RT. However, there is little evidence in the literature to support this theory.[126] Many tumors that recur after treatment (surgery, RT, or chemotherapy) are biologically more aggressive. Therefore, it is reasonable to treat these lesions with RT if surgery is not feasible.[127] The dose is essentially the same as that prescribed for other squamous cell carcinomas. Wang[128] reported a series of patients with verrucous carcinoma treated with RT; the results were comparable to those for patients treated for squamous cell carcinoma.

Results

Five-year DFS rates after RT range from 50% to 60%, depending on the stage of the primary lesion and the presence or absence of lymph node metastases.[62,128] Ash[62] reviewed the outcomes of 374 patients; 97% were initially treated with RT. The primary lesion was controlled in 52% of the patients; however only 25% of advanced lesions were controlled. Nair et al[129] evaluated the role of RT in the management of carcinomas of the buccal mucosa; RT was either administered with an interstitial implant consisting of 65 Gy over 6 days (45 patients), continuous course EBRT consisting of 52.5 Gy in

TABLE 32-15 Results of Radiotherapy in Cancer of the Buccal Mucosa: Site of Failure versus TN Category

UICC TN Category	Primary Failure No. (%)	Nodal Failure No. (%)	Total Failure No. (%)
T1N0	0/13 (0)	0/13 (0)	0/13 (0)
T2N0	13/49 (27)	7/49 (14)	18/49 (37)
T3N0	15/49 (31)	1/49 (2)	15/49 (31)
T4N0	6/12 (50)	1/12 (8)	7/12 (58)
Any T and N1	51/94 (54)	48/94 (51)	55/94 (59)
Any T and N3	12/17 (71)	15/17 (88)	14/17 (82)

Reprinted from Nair MK, Sankaranarayanan R, Padmanabhan TK, et al: Oral verrucous carcinoma. Treatment with radiotherapy. Cancer 61(3):458–461, 1988.

TABLE 32-16 Carcinoma of the Buccal Mucosa Treated Surgically: Primary Tumor Parameters versus Outcome

Clinical Factors	Patients	Recurrence
TUMOR CATEGORY		
T1	23	5 (22%)
T2	32	11 (34%)
T3	20	6 (30%)
T4	14	6 (43%)
THICKNESS		
<3 mm	18	4 (22%)
3 to 5.9 mm	26	6 (23%)
≥6 mm	26	14 (54%)
DEPTH OF INVASION		
<1 mm	13	2 (15%)
1 to 2.9 mm	18	6 (33%)
≥3 mm	22	12 (54%)
Total cases	89	28 (31%)

Reprinted from Urist MM, O'Brien CJ, Soong SJ, et al: Squamous cell carcinoma of the buccal mucosa: Analysis of prognostic factors. Am J Surg 154:411–414, 1987.

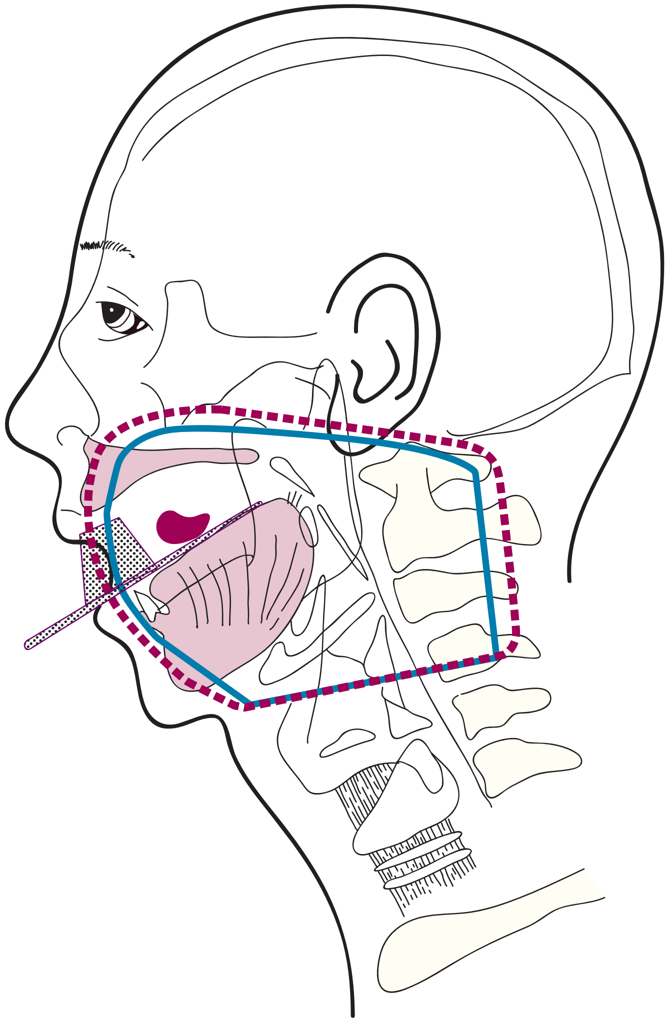


Figure 32-12 Buccal mucosa. Mixed ipsilateral en face 6-MV x-rays *(solid line)* and electrons *(dotted line)*. The electron field is 1 cm larger in all dimensions, as a result of beam constriction, except where it matches the anterior low neck field at the thyroid notch. *(Figure 1 from Mendenhall WM: Radiotherapy treatment technique. Cancer of the buccal mucosa. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Medical Publishers Inc.).*

15 fractions over 19 days or 60 Gy in 25 fractions over 33 days (139 patients), or as planned split-course EBRT consisting of 35 Gy in 15 fractions over 19 days—3-week split—25 Gy in 10 fractions over 12 days (46 patients). The split-course technique tended to be used in elderly patients or for those with massive tumors. The results are shown in Table 32-15. Relapse at the primary site increased with T stage.

Urist et al[130] reviewed results of 105 patients with squamous cell carcinomas of the buccal mucosa treated by resection of the primary tumor and neck dissection (Table 32-16). In a multivariate analysis, tumor thickness greater than 6 mm was the only significant prognostic factor. Depth of invasion greater than 3 mm was also highly significant but only in the univariate analysis.

Diaz et al[125] reported on 119 patients with buccal mucosal carcinomas treated at the M. D. Anderson Cancer Center (MDACC). Eighty-four were treated with surgery alone (71%), whereas 22 received postoperative RT and 13 received preoperative RT. None were treated with RT alone. Thirty-eight patients (32%) experienced local recurrences. Five-year OS by T category were T1, 79%; T2, 65%; T3, 56%; and T4, 69%. Muscle invasion, Stensen's duct involvement, and extracapsular spread of involved nodes were significantly associated with decreased survival.[125]

Techniques of Irradiation

T1 and T2

The patient is immobilized in the supine position with an aquaplast face mask. EBRT is administered with an ipsilateral field arrangement that includes the primary lesion and the levels I and II lymph nodes. The anterior and superior borders of the field should be at least 2 cm from the borders of the primary tumor. The posterior border should be at the posterior aspect of the spinous processes if the nodes are to be irradiated; the inferior border is at the thyroid notch. The oral commissures and lips are shielded if possible to reduce the acute effects. Patients may be treated with either a "wedge pair" of 6-MV x-ray beams or an en face "mixed beam" of 6-MV x-rays and electrons (Figure 32-12). The electron energy used in the mixed beam technique varies depending on the depth of the tumor. Because of the steep falloff of the electron beam at depth, it is preferable to risk overshooting rather than underdosing the deep extent of the tumor, and to use higher electron beam energies such as 15-MeV or 20-MeV beams. The EBRT dose fractionation schedule is 38.4 Gy at 1.6 Gy per fraction, twice daily. The ipsilateral low neck is treated with en face 6-MV x-ray field matched at the level of the thyroid notch.

If possible, a portion of the treatment should be given with intraoral cone irradiation or an interstitial implant to minimize the high dose volume and reduce the overall treatment time. Interstitial implantation is accomplished using ^{192}Ir via the plastic tube technique. The implant consists of a single plane of three to five horizontal tubes spaced 10 mm to 12 mm apart with crossing tubes at either end of the horizontal tubes. Ribbons containing ^{192}Ir seeds are afterloaded into the tubes to deliver approximately 30 Gy to 35 Gy at 10 Gy to 12 Gy per day specified at 5 mm from the plane of the sources after EBRT.

T3 and T4 Lesions

Well-lateralized tumors may be treated with the ipsilateral field arrangement as previously described. Patients with significant tumor extension toward the midline are treated with parallel-opposed fields weighted 3:2 toward the side of the lesion. Field reductions occur at 40.8 Gy to 45.6 Gy and at 60 Gy. The clinically negative low neck is treated with an anterior field with a 6-MV x-ray beam to 50 Gy in 25 fractions once daily. Thereafter, part or all of the low neck may be boosted depending on the presence and location of clinically positive neck nodes. IMRT may be considered, depending on the extent of the lesion, to optimize tumor coverage while limiting the dose to adjacent critical structures such as the cerebellum and temporal lobe.

For postoperative RT, the target volume includes the primary tumor bed and ipsilateral submandibular (level I) and subdigastric (level II) nodes. Patients with extensive positive ipsilateral nodes should be considered for RT to both sides of the neck. Patients with a tumor category of T2 or higher, tumor thickness more than 6 mm, or depth of invasion more than 3 mm have a greater than 30% risk of local recurrence, and should be treated with postoperative RT.[130]

Patients with advanced cancers unsuitable for aggressive therapy are treated with palliative RT. The fractionation scheme is either 20 Gy in 2 fractions with a 1-week interfraction interval, or 30 Gy in 10 fractions over 2 weeks.

Complications

The buccal mucosa tolerates high-dose RT with a low risk of late complications. Trismus may develop if the muscles of mastication receive high doses of RT.

GINGIVA

Anatomy

The gingiva is composed of fibrous tissue covered by mucous membrane that is firmly attached to the periosteum of the alveolar processes of the mandible and maxilla. The lower gingiva includes the mucosa covering the mandible from the gingival-buccal gutter to the origins of the mobile mucosa on the floor of the mouth. There are no minor salivary glands in the mucous membranes of the alveolar ridges.

The gingiva receives sensory innervation from the nerves supplying the teeth that are branches of cranial nerves V2 and V3 (buccal, infraorbital, greater palatine, and mental nerves).

Pathology and Patterns of Spread

Squamous cell carcinomas are most common, usually arise from the posterior portion of the mandibular gingiva, and are often associated with leukoplakia. Verrucous carcinomas may also occur, usually on the lower gingiva.

Squamous cell carcinomas of the mandibular gingiva may invade the underlying bone, retromolar trigone, adjacent buccal mucosa, and floor of the mouth. Byers et al[131] reported that 22% had associated leukoplakia, 36% had mandibular invasion, and 5% had perineural involvement. Bone invasion usually starts because there is no complete bony barrier in the edentulous portion of the mandible. The lingual and buccal plates are relatively resistant to tumor penetration. Tumor entry through the mental, mandibular, and other small foramina tend to occur in less than 10% of patients.[132]

Metastatic spread occurs first to the submandibular (level I) and upper internal jugular (level II) lymph nodes. Byers et al[131] reported 16% clinically positive nodes at diagnosis; contralateral lymph node involvement was found in only 3% of cases. Subclinical lymph node disease has been reported in 17% to 19% of cases.[131] The incidence of involved lymph nodes was 12% for T1 and T2 lesions, and 13% for T3 and T4 stage cancers.[65] The distribution of positive lymph nodes after elective neck dissection is shown in Figure 32-13.[65]

Clinical Manifestations and Staging

The patient with squamous cell carcinoma of the gingiva may first present to the dentist with ill-fitting dentures, pain, loose teeth, or a sore that will not heal. Intermittent bleeding and pain may occur when the lesion is traumatized. Invasion of the inferior dental nerve may produce paresthesia or anesthesia of the lower lip.

Because bone invasion compromises the results of RT, careful radiographic examination of the mandible with panoramic x-ray films, dental radiographs, and CT scan is essential. The AJCC staging system is shown in Table 32-2.[31]

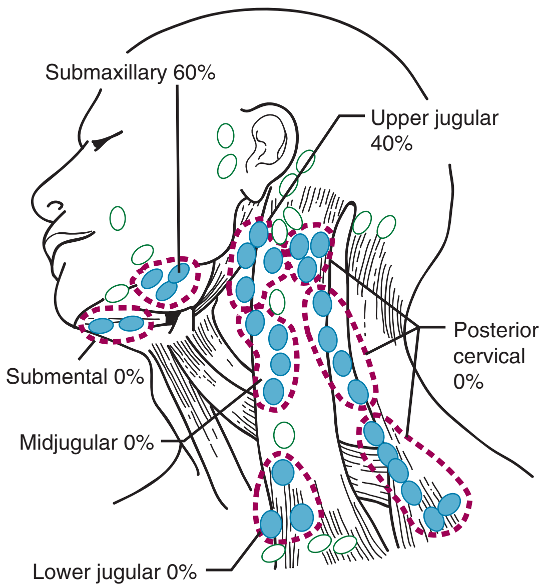


Figure 32-13 Carcinoma of the gingiva. The distribution of involved lymph nodes after elective modified neck dissection for patients with a clinically negative neck.
(From Byers RM, Wolff PF, Ballantyne AJ: Rationale for elective modified neck dissection. Head Neck Surg 10:163, 1988).

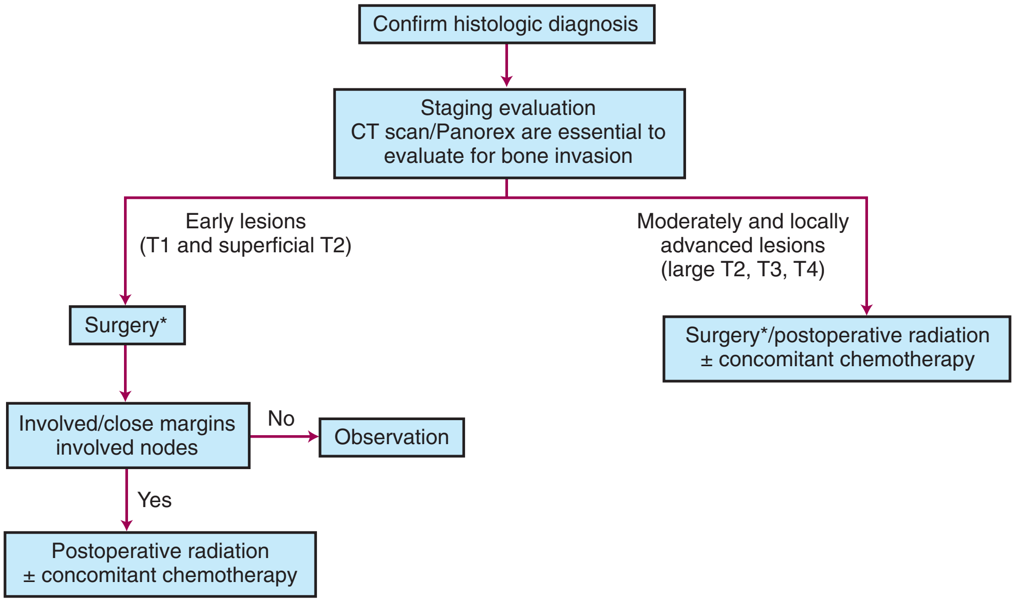


Figure 32-14 **Treatment algorithm for de novo gingival cancer.** *Treat neck (neck dissection).[65,131]

Treatment

Early Lesions (T1 and Superficial T2 Lesions)

The majority of these lesions are managed by surgery. Small lesions may be removed by transoral resection; however, rim resection is necessary in most cases. When direct bone invasion is present, removal of a segment of the mandible (segmental mandibulectomy) or maxilla is required. A treatment algorithm is shown in Figure 32-14.

Moderate to Locally Advanced Lesions (Large T2, T3, and T4 Lesions)

Large lesions may require a segmental mandibulectomy or partial maxillectomy.[133] Because of the likelihood of local invasion through or along the subperiosteal lymphatics, RT is often indicated after resection to eradicate microscopic disease at the margins, to sterilize subclinical disease in the cervical lymph nodes, and thus improve the likelihood of cure.[33] Postoperative RT is also indicated in the presence of perineural invasion and extensive nodal disease (large node(s) or multiple positive nodes or extranodal extension).[53] Concomitant chemotherapy during EBRT is also recommended in the postoperative setting, as outlined elsewhere in this chapter.

Results

Cady and Catlin[133] reviewed 606 patients with squamous cell carcinoma of the gingiva treated by surgery. The survival rate was 43% for patients with mandibular gingival lesions and 40% for those with maxillary alveolar ridge cancers. Soo et al[134] reviewed a 20-year experience with squamous carcinoma of the gums in 347 patients treated at the MSKCC. Sixty-four percent of patients presented with a clinically negative necks (N0). Ninety-seven percent of patients were treated surgically. The 5-year CSS was 54%. Advanced clinical stage (stages III and IV), prior dental extractions, bone invasion, and involvement of surgical margins were predictive of a lower survival rate on univariate analysis. Clinical stage was the only significant predictor of survival on multivariate analysis.

Byers et al[131] reported a 5-year OS of 43% for patients with squamous cell carcinoma of the mandibular gingiva. Fifty-one of these patients were treated with surgery that included resection of bone in 28 patients with early lesions. Only 1 of 28 patients developed a recurrence. Segmental mandibulectomy and neck dissection were used for 23 patients with advanced disease; there were no local failures. Postoperative RT was given for close margins, nerve invasion, or extensive nodal metastases (large nodes, multiple nodes, or extracapsular extension). For those treated with surgery and postoperative RT, control above the clavicles was achieved in 95% of patients.

Overholt et al[135] retrospectively reviewed results of 155 patients treated surgically for carcinoma of the mandibular gingiva. Decreased local control was observed for primary lesions larger than 3 cm ($p = 0.021$) and persistently positive surgical margins ($p = 0.027$). Survival was adversely affected by advanced T category ($p = 0.001$), positive initial and final surgical margins ($p = 0.004$), mandibular invasion ($p = 0.014$), and cervical metastases ($p < 0.001$). Local control and survival were not affected by extent of mandibular resection, tumor extension beyond the mandibular gingiva, recent dental extractions in the region of the primary tumor, perineural invasion, or histologic grade.

Patients treated with RT alone for T3 and T4 lesions have 5-year OS ranging from 30% to 40%.[123,131] Wang[128] reported a 78% control rate for patients with T1 lesions and 27% for those with T2 cancers after treatment with RT alone. Fayos[136] reported a 50% local control rate after RT alone for lesions with early bone invasion and a 25% local control rate after RT alone for those with extensive invasion.

Techniques of Irradiation

T1 and T2 Lesions

Patients who are not deemed to be surgical candidates are treated with RT. Small lesions may be treated by intraoral cone RT combined with EBRT. Interstitial implant has no place in the management of this disease because of the proximity of the bone and the high risk of osteoradionecrosis.

EBRT may be administered with either an ipsilateral en face combination of 4-MV or 6-MV x-rays and electrons, or with two 4-MV or 6-MV x-ray beams arranged in a wedge pair (Figure 32-15). The latter technique is preferred because it is possible to vary the depth of the target volume more precisely,

Figure 32-15 Patient with an early-stage carcinoma of the retromolar trigone. Radiotherapy is delivered with two 6-MV x-ray beams via a "wedge-pair" arrangement.
(Figure 1 from Mendenhall WM: Radiotherapy treatment technique. Cancer of the maxillary alveolar ridge and retromolar trigone. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Publishing.)

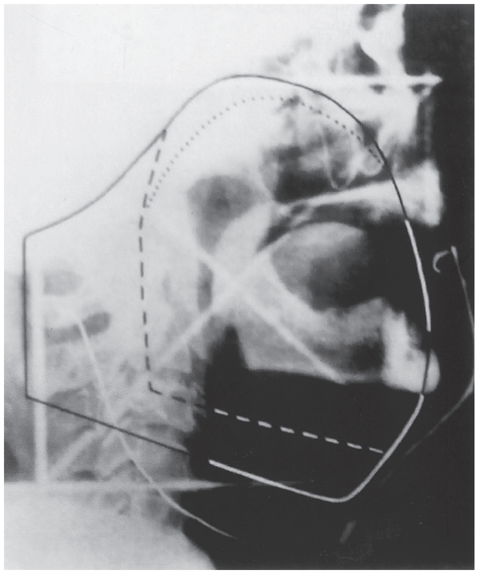


Figure 32-16 Typical portal for irradiation after hemimandibulectomy, partial maxillectomy, and radical neck dissection for pathologic T4N0 retromolar trigone lesion. **(A)** Field reductions made at 45 Gy *(dashed line)* and 60 Gy *(dotted line)*.
(Figure 2 from Amdur RJ1, Parsons JT, Mendenhall WM, et al: Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 16(1):25-36, 1989.)

and underdosing the medial extent of the tumor is less likely. Lesions that exhibit significant extension onto the soft palate, or into the tongue (unusual for a T1 or T2 tumor) would be treated with parallel-opposed fields weighted 3:2 to the side of the tumor. Alternatively, IMRT may be employed to spare the contralateral parotid. The doses used are from 60 to 65 Gy over 6 to 6½ weeks for T1 tumors, and 70 Gy over 7 weeks or 74.4 Gy in 62 fractions twice daily for T2 tumors. The low neck (levels III and IV) is treated with an anterior 4-MV or 6-MV x-ray field matched at the thyroid notch and receives 50 Gy in 25 fractions.

T3 and T4 Lesions

Patients with T3 and T4 carcinomas have a relatively low chance of cure with RT alone and are optimally treated with surgery and postoperative RT. The postoperative dose varies with the margins. Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Altered fractionation is considered for patients with positive margins and for those with multiple risk factors or a prolonged interval between surgery and radiation therapy. At our institution, the preferred schedule is 74.4 Gy at 1.2 Gy per fraction administered twice daily in a continuous course over 6.5 weeks. As with other sites, concomitant cisplatin is also recommended for high-risk situations.

Patients are treated with parallel-opposed portals that include the primary tumor and upper neck nodes (levels I and II) (Figure 32-16). The fields are weighted 3:2 toward the side of the tumor. The anterior low neck (levels III and IV) is treated with an en face 6-MV x-ray field matched at the level of the thyroid notch. A petroleum jelly gauze bolus is placed on the incisions to ensure an adequate surface dose. Fields are reduced off of the spinal cord at approximately 45 Gy. An electron beam may be used to irradiate the posterior neck (level V) if additional RT to these sites is indicated after off-cord reduction.

Patients who are not suitable for surgery are treated with twice-daily EBRT to 76.8 Gy in 64 fractions over 6.5 weeks combined with concomitant chemotherapy. The field arrangements are similar to those previously described. We routinely exclude the spinal cord at 40 Gy if chemotherapy is used concomitantly. IMRT may be used to reduce the dose to the contralateral parotid unless bilateral positive nodes are present. Patients who are unsuitable for aggressive treatment receive moderate dose palliative RT; 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1 week interfraction interval.

For postoperative cases, radiation volumes include the adjacent segment of the mandible or maxilla. The entire hemimandible or hemimaxilla from the distal neural foramen to the pterygopalatine ganglion must be treated when perineural invasion is present. The low neck must be irradiated if involved nodes are present or if the primary tumor is advanced. Postoperative EBRT doses range from 60 Gy to 75 Gy at 1.8 Gy to 2.0 Gy per day. If the resection margins are positive, 74.4 Gy at 1.2 Gy per fraction, twice daily with a minimum 6-hour interfraction interval is currently used at our institution. Cisplatin is administered concomitantly, based on the results of recently published randomized data from the RTOG and EORTC.[50,52]

Complications

Surgical complications include orocutaneous fistulae and bone exposure. The complications of RT include dental caries, soft-tissue necrosis, and osteoradionecrosis. The risk is greatest for more advanced lesions.

RETROMOLAR TRIGONE

Anatomy

The small triangular surface posterior to the third mandibular molar, overlying the ascending ramus is called the *retromolar trigone*. Beneath the mucosa of the retromolar trigone is the pterygomandibular raphe, which is attached to the pterygoid hamulus on the posterior mylohyoid ridge of the mandible. It serves as the insertion of the buccinator and superior constrictor muscles. Behind the pterygomandibular raphe (between the medial pterygoid muscle and the ascending ramus of the mandible) is the pterygomandibular space, which contains the lingual and dental nerves. There is a small fat pad between the pterygoid muscle group and the mandibular foramen through which the mandibular nerve passes before it enters the alveolar canal. The subdigastric lymph (level II) nodes are the first echelon nodes for the retromolar trigone.

Pathology and Patterns of Spread

The vast majority of these tumors are squamous cell carcinomas. The primary tumor may spread to the adjacent buccal mucosa, anterior tonsillar pillar, mandibular gingiva, and mandible. Posterior spread to the pterygomandibular space and medial pterygoid muscle may occur. Invasion of the periosteum may occur early. Byers et al[137] reported a 25% incidence of bone invasion at diagnosis.

The incidence of clinically positive ipsilateral nodes on presentation is 39% and the risk of subclinical disease in the cervical lymph nodes is approximately 25%.[137] The distribution of positive nodes after an elective neck dissection is shown in Figure 32-17.[65]

Clinical Manifestations and Staging

Retromolar trigone cancers tend to produce pain that may be referred to the external auditory canal and preauricular area. Invasion of the pterygoid muscles can produce trismus and is better demonstrated by MRI than by CT.[66] CT scan of the head and neck (and MRI in selected cases) is useful for determining the deep extent of the primary tumor, bone invasion, and presence of positive neck nodes. The staging system is depicted in Table 32-2.

Treatment

Early Lesions (T1 and T2 Lesions)

Local control rates for T1 and T2 lesions are similar following surgery or RT.[137] If the tumor extends to the tonsillar pillar, soft palate, or buccal mucosa, and an extensive resection is required, RT is selected. If possible, intraoral cone irradiation should be used for a portion of the treatment. Small lesions without detectable bone invasion can be resected with removal of the periosteum or a rim resection of the mandible. A treatment algorithm is shown in Figure 32-18.

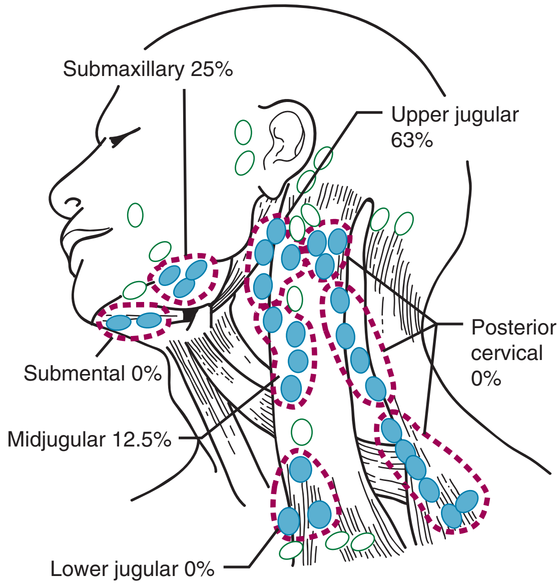


Figure 32-17 Carcinoma of the retromolar trigone. The distribution of involved lymph nodes after elective modified neck dissection for patients with a clinically negative neck.
(From Byers RM, Wolf PF, Ballantyne AJ: Rationale for elective modified neck dissection. Head Neck Surg 10:163, 1988.)

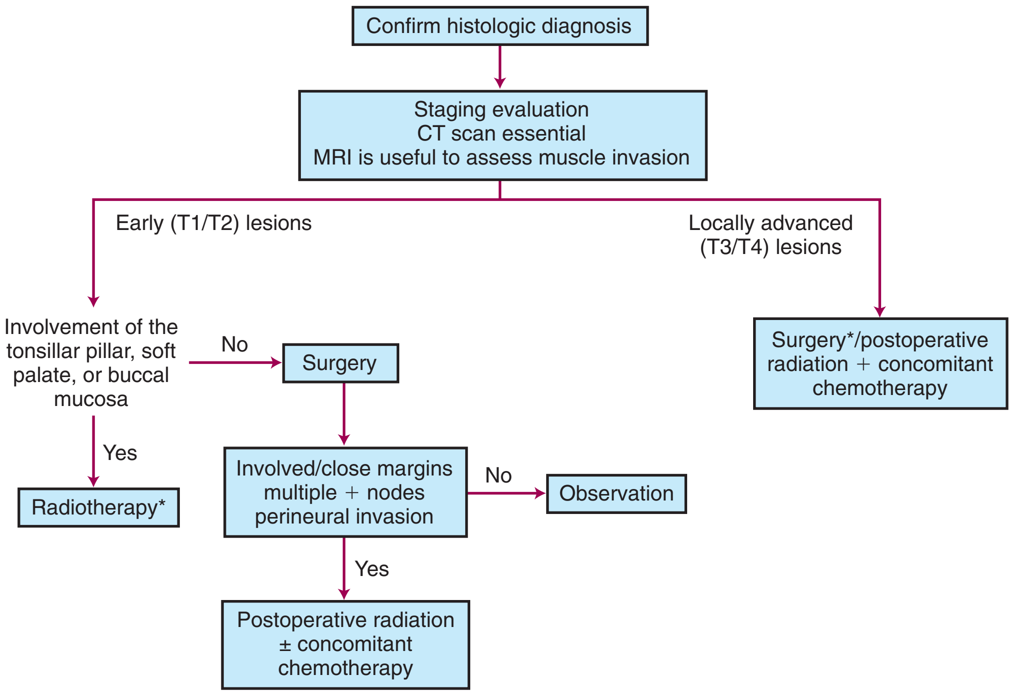


Figure 32-18 Treatment algorithm for de novo retromolar trigone cancer. *Treat neck (radiotherapy or neck dissection).

Locally Advanced Lesions (T3 and T4)

Superficial T3 lesions can be treated by RT. Locally advanced cancers (especially those with evidence of bony invasion) require a segmental mandibulectomy followed, in almost all cases by postoperative RT.

Results

Lo et al[138] reported on a series of patients treated with RT at the MDACC (Table 32-17). Patients with retromolar trigone cancers were grouped with those having anterior tonsillar pillar lesions. Local control varied from 70% to 76% after RT for those with T1, T2, and T3 cancers. Salvage surgery resulted in ultimate local control rates varying from 92% to 100%.

Mendenhall et al reported on 99 patients treated with RT alone or combined with surgery at the University of Florida.[139] The likelihood of cure was influenced by extent of disease and treatment; those treated with surgery and RT had a better chance of cure than those treated with RT alone (Table 32-18).

Kowalski et al[140] reported on 114 patients who underwent an extended "commando" operation between 1960 and 1991 for carcinoma of the retromolar trigone. Sixty-six patients received postoperative RT (median 50 Gy). Tumor categories were: T1, 5 patients; T2, 44 patients; T3, 24 patients; T4, 28 patients; and TX, 13 patients. Forty-one patients (36%) experienced a recurrence at one or more sites: local 31 (27%); dissected neck, 9(22%); contralateral neck, 3 (7%); and distant, 7 (17%). The 5-year overall survival rates by T stage were: T1, 80.0%; T2, 57.8%; T3, 46.5%; T4, 65.2%, and overall, 55.3%.

Byers et al[137] reported on 110 patients with squamous carcinoma of the retromolar trigone who were treated at the MDACC from 1965 to 1977 and followed for ≥5 years. Seventy patients had T1 and T2 tumors, and 77 patients had a clinically negative neck. Sixty patients received either surgery alone (n = 46) or combined with preoperative or postoperative RT (n = 14). Fifty patients were treated with RT alone. Failure at the primary site occurred in 7 of 60 patients (12%) treated surgically, and in 8 of 50 patients (16%) of patients treated with RT alone.

Techniques of Irradiation

Treatment techniques for retromolar trigone cancers are similar to those discussed in the preceding section on gingival cancers.

Complications

Thirty percent of the patients reported by Lo et al[138] developed some degree of bone exposure but only 9 patients (5.6%) required a segmental mandibulectomy. The probability of bone exposure was not found to be dose related. Huang et al[141] reported on 65 patients treated for retromolar trigone cancer and observed complications that included bone necrosis, soft-tissue necrosis, and severe trismus, occurring in 12% after surgery and postoperative RT, 11% after RT alone, and none after preoperative RT and surgery.

Kowalski et al[140] observed complications in 51.8% of 114 patients who underwent an extended commando operation between 1960 to 1991; 21 patients (18.4%) had a wound infection.

HARD PALATE

Squamous cell carcinoma of the hard palate is relatively rare. In a series of about 5000 patients with oral cavity cancers, only 25 patients (0.5%) had squamous cell carcinoma of the hard

TABLE 32-17 Local Control Rates after Radiotherapy: Anterior Faucial Pillar-Retromolar Trigone—M. D. Anderson Hospital

Category	Local Control	Treatment of Primary Failure	No. Patients Salvaged	Ultimate Control Rate
T1	12/17 (71%)	Surgery (5)*	5/5	17/17 (100%)
T2	57/81 (70%)	No treatment (2) Surgery (21) Surgery + RT (1)	19/24†	76/81 (94%)
T3	19/25 (76%)	Surgery (5) Surgery + Chemo (1)	4/6†	23/25 (92%)
T4	3/5	Surgery (1) Chemo (1)	1/2†	4/5

Reprinted from Lo K, Fletcher GH, Byers RM, et al: Results of irradiation in the squamous cell carcinomas of the anterior faucial pillar-retromolar trigone. Int J Radiat Oncol Biol Phys 13:969–974, 1987.
Chemo, *Chemotherapy;* RT, *radiotherapy.*
**Numbers in parentheses indicate number of patients.*
†Five T2 patients, one T3 patient, and one T4 patient died in less than 2 years with no evidence of local disease.

TABLE 32-18 Local Control of Squamous Cell Carcinoma of the Retromolar Trigone Treated at the University of Florida

	Definitive Radiation			Surgery + Radiation			Total		
T Category	No. Pts.	No. Local Recurrences	5-Year LC	No. Pts.	No. Local Recurrences	5-Year LC	No. Pts.	No. Local Recurrences	5-Year LC
T1-T3	26	13	49%	31	6	78%	57	19	65%
T4	9	6	44%	33	11	65%	42	17	61%
Total	35	19	48%	64	17	71%	99	36	63%

Reprinted from Mendenhall MW, Morris CG, Werning JW, et al: Retromolar trigone squamous cell carcinoma treated with radiotherapy alone or combined with surgery. Cancer 103(11):2320–2325, 2005.
LC, *Local control.*

palate.[142] In a similar study, carcinoma of the hard palate represented 3% of all oral cavity carcinomas.[143]

The male-to-female ratio is approximately 1:1. For both males and females, the peak incidence tends to occur in the seventh decade, with more than 98% of patients older than the age of 40.[144]

Anatomy

The palate forms the roof of the oral cavity and the floor of the nasal cavity. The anterior two thirds, or bony part of the palate, is called the hard palate and is formed by the palatine processes of the maxilla and the horizontal plates of the palatine bones. Anteriorly and laterally, the hard palate is bounded by the maxillary alveolar ridge and gingiva. Posteriorly, the hard palate is contiguous with the soft palate. The hard palate is covered by a mucous membrane overlying the periosteum. Deep to the mucosa are the secreting palatine glands. The incisive foramen is posterior to the maxillary central incisors; the nasopalatine nerves pass through this foramen.

The greater palatine foramina are medial to the third maxillary molars; the greater palatine vessels and nerves emerge from this foramen. The greater palatine nerve innervates the gingiva, mucous membrane, and glands of the hard palate. The nasopalatine nerve innervates the mucous membrane of the anterior part of the hard palate. Because of the rich blood supply from the greater palatine artery, the incidence of osteoradionecrosis and soft-tissue necrosis is lower than that reported for the mandible.[145]

Pathology and Patterns of Spread

Malignant tumors of the hard palate are most often adenoid cystic carcinomas and mucoepidermoid carcinomas arising from minor salivary glands. Squamous cell carcinoma is relatively uncommon. Kaposi's sarcoma and melanomas may also originate from the mucosa of the hard palate.[144]

Most squamous cell carcinomas originate on the gingiva and spread secondarily to the hard palate. Perineural invasion occurs via the greater palatine foramen. The risk of positive lymph nodes is 13% to 24% at diagnosis.[146,147] The incidence of subclinical disease in the cervical lymphatics is 22%.[62]

Clinical Manifestations, Patient Evaluation, and Staging

Patients with squamous cell carcinomas of the hard palate may first present to the dentist with ill-fitting dentures, pain, loose teeth, or a sore that will not heal. Intermittent bleeding and paresthesias may also occur.

Imaging of the hard palate is primarily with CT scanning and is occasionally supplemented with MRI. Imaging of the neck nodes must include the facial and retrozygomatic nodes.[66] Facial nodes are best assessed by bimanual examination, particularly in patients with dental fillings. If the lesion is an adenoid cystic carcinoma, it is essential to search for perineural spread. The AJCC staging system is shown in Table 32-2.[31]

Treatment

Surgery is the usual initial treatment for most lesions; postoperative RT is indicated for patients with more extensive cancers. The role of primary RT in the management of hard palate carcinomas is ill defined. If the lesion has a large surface area and is superficial, RT can be used as initial treatment. However, most patients are treated with surgery because the underlying bone is often involved and, in that scenario, RT is unlikely to be effective.[148] Postoperative RT is indicated for

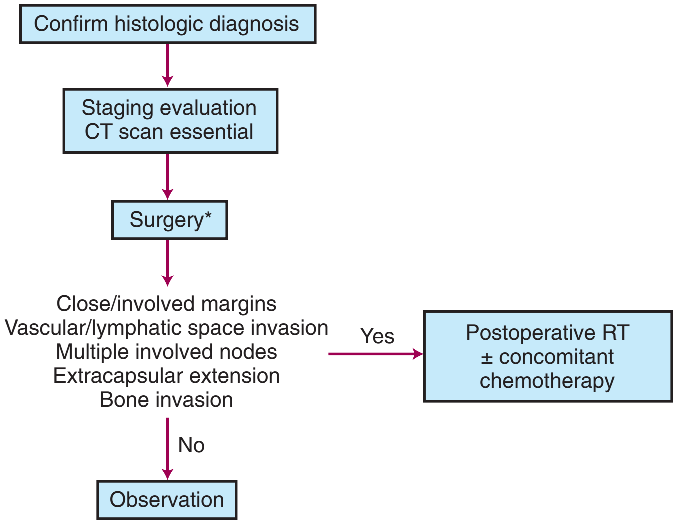


Figure 32-19 **Treatment algorithm for de novo hard palate cancer.** *Treat neck (neck dissection).

close or involved margins, perineural or vascular invasion, multiple involved nodes, extracapsular extension, or bone invasion.[53] Dose and fractionation recommendations are similar to those given for other sites. A treatment algorithm is shown in Figure 32-19.

Malignant salivary gland tumors of the hard palate are often treated by a combination of surgery and postoperative RT, particularly if they are high-grade tumors (adenocarcinoma, salivary duct carcinoma, high-grade mucoepidermoid, myoepithelial carcinoma, others?). Low-grade (acinic cell carcinoma, adenoid cystic carcinoma, low-grade mucoepidermoid) minor salivary gland carcinomas can be treated by surgery alone if negative margins can be achieved. Some malignant minor salivary gland tumors have been successfully controlled by high-dose RT alone.[149]

Results

Shibuya et al[150] reported the RT results for malignant lesions of the hard palate; the 5-year OS for those with squamous cell carcinomas was approximately 45%. For patients with minimal bone invasion and clinically negative neck, the 5-year OS was 75%. Data from the University of Virginia are presented in Table 32-19 for 41 patients treated with surgery, RT or both.[151]

Yorozu et al[152] reported on 31 patients treated with EBRT at the Christie Hospital between 1990 and 1997. Twenty-six received RT alone and five were treated postoperatively for positive surgical margins. The 5-year local and ultimate local control rates after salvage surgery were 53% and 69%, respectively. Survival rates were 48% for patients with squamous carcinomas and 63% for those with minor salivary gland carcinomas. T category was the only significant predictor of 5-year local control rates, which were 80% for T1 and T2 lesions and 24% for T3 and T4 lesions, respectively. The only significant predictor for survival was N category.

Tran et al[153] reported on 38 patients treated for salivary gland tumors of the palate at University of California at Los Angeles. Twenty-three of 38 tumors were on the hard palate; adenoid cystic carcinoma was the most common histologic type. Twenty-five patients received surgery alone; 13 were treated with surgery and postoperative RT. The local control rates were comparable for the two groups of patients (88% and 85%, respectively).

TABLE 32-19 Hard Palate Malignancies Treated by Surgery, Radiotherapy, or Both: 5- and 10-Year Survival Rates

	5-Year		10-Year	
Histology	**Absolute**	**Cause-Specific**	**Absolute**	**Cause-Specific**
Squamous cell carcinoma	10/26 (38%)	10/17 (59%)	8/25 (32%)	8/15 (53%)
Salivary gland tumors				
Adenocarcinoma	5/7 (71%)	5/7 (71%)	3/6 (50%)	3/5 (60%)
Adenoid cystic carcinoma	3/3	3/3	1/2	1/1
Malignant mixed tumor	5/5	5/5	1/4	1/1

Reprinted from Chung CK, Johns ME, Cantrell RW, et al: Radiotherapy in the management of primary malignancies of the hard palate. Laryngoscope 90:576–584, 1980.

Kovalic et al[154] reported on 13 patients with carcinoma of the hard palate treated at Washington University. Histologic types included adenoid cystic carcinoma, 9 patients; squamous cell carcinoma, 3 patients; and mucoepidermoid carcinoma, 1 patient. T-stages were T1, 1 patient; T2, 5 patients; T3, 3 patients; and T4, 4 patients. All had a clinically negative neck. Ten patients received excision and postoperative RT; 3 patients were treated with RT alone. The 10-year DFS and local control rates were 77% and 92%, respectively.

A group of 50 patients was treated surgically at the University of Cincinnati and included 25 patients with squamous cell carcinomas, 11 with adenoid cystic carcinomas, 6 with adenocarcinomas and 8 with miscellaneous histologies.[155] The 5-year OS by histology were squamous carcinoma, 76%; adenoid cystic carcinoma, 90%; and overall, 85%. The 10-year OS for adenoid cystic carcinomas fell to 75%, consistent with their tendency to develop late recurrences, including distant metastases.

Most relapses are found at the primary site. Evans and Shah reported a 53% incidence of isolated primary site failure.[144] The incidence of recurrence in the cervical nodes was 30%; failure involving both the primary site as well as the cervical lymph nodes was 10%. No patient treatment failed with results of distant metastases only. Seven percent of the patients experienced treatment failure in both distant and local regional sites.[144]

The risk of developing metachronous carcinomas is high. In the University of Virginia's experience, 28% of the patients developed a metachronous primary carcinoma during their lifetime and 13% developed a third, fourth, or fifth carcinoma. The oral cavity was the most common site for metachronous cancers.[146]

Techniques of Irradiation: Hard Palate and Maxillary Alveolar Ridge

T1 and T2 Lesions

The preferred initial treatment for patients with T1 and T2 carcinomas of the hard palate is surgery. RT is used by default to treat the occasional patient who is not a surgical candidate. Most of these lesions are not well lateralized, consequently, RT is administered with parallel-opposed fields encompassing the primary tumor with a margin of 2 cm or less. A cork-and-tongue block is placed in the mouth to displace the tongue, mandible, and lower lip inferiorly and to reduce the amount of normal tissue included in the fields (Figure 32-20, *A*). These lesions are not amenable to brachytherapy and so patients are treated with EBRT alone. The likelihood of cure with RT alone, even for early-stage lesions, is relatively low so that an altered fractionation technique should be employed. We prefer hyperfractionated RT and use 74.4 Gy to 76.8 Gy at 1.2 Gy per fraction, twice daily, over 6 to 6.5 weeks. The volumes are extended to include the regional lymph nodes (levels I and II) for patients with aggressive, poorly differentiated cancers (see Figure 32-20, *B*). The disadvantage of irradiating the regional lymph nodes is that the acute toxicity of the treatment is significantly increased. Fields are reduced at 45.6 Gy in 38 fractions to limited portals that adequately encompass the primary cancer. The low neck (levels III and IV) is irradiated with an anterior field that abuts the primary fields at the level of the thyroid notch and receives 50 Gy in 25 fractions over 5 weeks.

T3 and T4 Lesions

Patients with T3 and T4 cancers are optimally treated with surgery and postoperative RT using fields encompassing the primary tumor and regional lymph nodes as previously described. Postoperative RT is initiated within 6 weeks of surgery. Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Reduction off of the spinal cord is performed at 44 Gy to 46 Gy and the posterior strips are treated with 8 MeV to 10 MeV elections if it is necessary to irradiate these areas to a higher dose. An altered fractionation technique should be considered for those who have positive margins, multiple risk factors, or a prolonged surgery-RT interval.[53] Systemic cisplatin chemotherapy is usually administered concomitantly with RT in the postoperative setting.[50,52]

Patients with T3 and T4 cancers who are not surgical candidates have a low chance of cure with RT. Patients are treated to 76.8 Gy at 1.2 Gy per fraction twice daily over 6.5 weeks combined with concomitant chemotherapy such as weekly cisplatin 30 mg/m^2. Patients who are not candidates for aggressive therapy are treated with moderate dose palliative RT over 1 to 2 weeks.

Complications

No severe complications occurred in the patients who received RT (60 Gy in 5 to 6 weeks) at the University of Virginia.[151] Most patients developed xerostomia and temporary loss of taste.[146]

Yorozu et al[152] reported results for 31 patients treated with EBRT at the Christie Hospital between 1990 and 1997. Twenty-six patients received RT alone and five were treated postoperatively for positive surgical margins; necrosis occurred in 1 patient.

CONCLUSIONS AND FUTURE POSSIBILITIES

Treatment algorithms by site within the oral cavity are covered in the separate site presentations and discussions within this chapter. In general, early lesions at any site in the oral cavity can be treated by single modality treatment with excellent results. As lesions become more extensive, the need for combined modality treatment increases (i.e., surgery plus RT with or without chemotherapy, RT plus concomitant chemotherapy, or all three modalities). Future trials should address issues of sequencing when combined modality treatment is indicated,

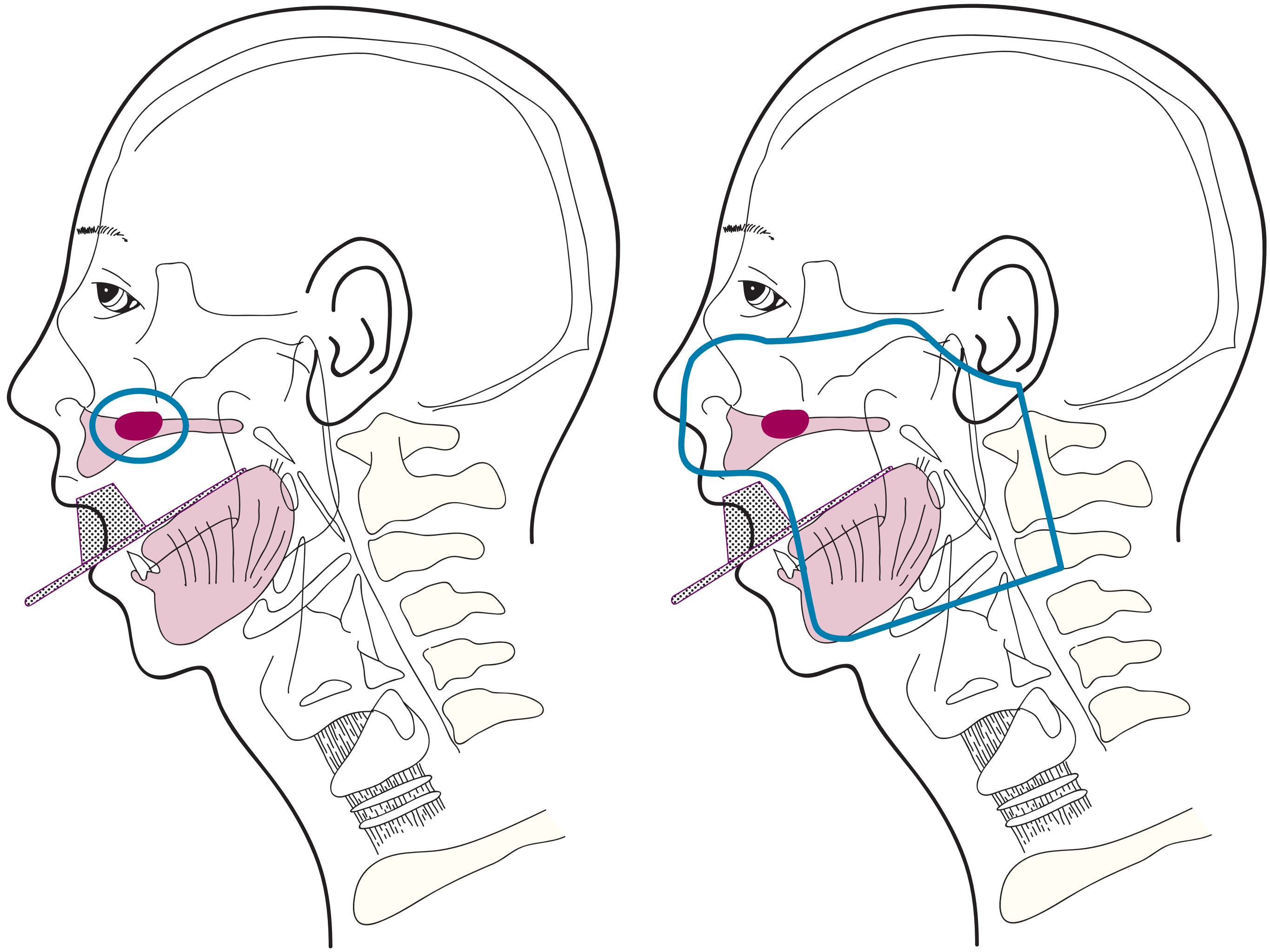


Figure 32-20 **A,** Early-stage hard palate carcinomas. Parallel-opposed 6-MV x-ray fields include the tumor with a 2-cm margin. Cork-and-tongue block displace the tongue and mandible inferiorly to minimize the amount of normal tissue included in the fields. **B,** Advanced hard palate carcinoma. Portals include the primary tumor and upper neck nodes (levels I and II). The superior margin of the portals is extended to include V_2 to the skull base.
(Figure 2 from Mendenhall WM: Radiotherapy treatment technique. Cancer of the maxillary alveolar and hard palate. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Publishing; Cancer of the maxillary alveolar and hard palate. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Publishing, Figures 1 and 2.)

as well as the need for concomitant chemotherapy when altered fractionation RT is employed and the optimal chemotherapy agents and regimen (cisplatin, cetuximab, docetaxel alone, or combined).

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