Oral Cancer Treatment

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Opinion statement

Oral cancer is the sixth most common cancer in the world, and it continues to represent a serious public health problem. Oral cancer is a preventable disease, related to behavioral and lifestyle factors, including tobacco and alcohol. Prevention and early detection of oral cancer remain the goals of national efforts to reduce the impact of this disease on the public. Surgical treatment is the mainstay of therapy for patients with oral cancer, particularly in advanced stages of cancer. External beam radiation therapy and brachytherapy have been used successfully as the primary modality for treating patients with early stage oral cancer, and they are the standard of care for use as adjuvant therapy in postoperative cases of patients with advanced stage oral cancer. There is an emerging trend for the use of chemotherapy in combination with radiation therapy and surgery for patients with advanced, recurrent, and metastatic head and neck cancer, although evidence is limited regarding survival benefit when used for treating patients with oral cavity carcinoma. Any report on the treatment of oral cancer is incomplete without consideration of functional and aesthetic outcomes, particularly addressing speech, swallowing, masticatory efficiency, and dental rehabilitation. Future generations will continue to fight these dreadful diseases until scientists and clinicians are provided the opportunities to expand efforts to prevent, detect (early), and eradicate oral and other head and neck cancers.

Introduction

Cancers of the oral cavity and oropharynx are diagnosed in approximately 30,000 people in the United States each year, with approximately 8000 people dying from the disease. These rates involve squamous cell carcinoma, and there appears to be disparities in incidence and survival data among race and gender, with black males having higher incidence and mortality rates in some regions. Oral cavity cancers (OCC) are two to four times more likely to be found in male than in female persons, and older age (> 55 years) is associated with higher rates [1].

The lip, tongue, and floor of the mouth are the most common sites of OCC in the United States, with other sites more commonly diagnosed in different countries, varying by geographic regions, ethnicity, and exposure to risk factors. Changes and trends in demographic distribution, incidence, and survival rates of patients indicate little change in early detection or in 5-year survival rates (50%) of patients over the past 30 years [2,3•,4]. An unexplained increase in tongue cancer occurred in young adult birth cohorts from 1938 to 1948, and younger age groups have a higher percentage of tongue and palate cancer, according to the National Cancer Database Report [5].

Treatment

Diet and lifestyle

- Tobacco smoking is associated consistently with a higher risk of developing OCC compared to not smoking [6]. Various tobacco products, including smokeless tobacco, have been implicated in the etiology of these cancers, often varying by demographic differences. Exposure to sunlight has been blamed for squamous cell carcinoma of the lower lip. Although studies have shown a prevalence of human papillomavirus (HPV; 34.5%) in head and neck squamous cell carcinoma (HNSCC), with the oral cavity being the most common site, a recent study showed a survival advantage for patients with HPV and wild-type *p53* malignant cells. More than 50% of HPV-positive tumors in this study were type 16 [7]. Heavy alcohol consumption is associated with OCC; however, its role in people who develop OCC is unclear [6]. Diet and lifestyle remain important factors in the development of these cancers. Evidence exists that OCC may be related to various forms of tobacco, second-hand smoke, and marijuana. A history of OCC and low intake of fruits and vegetables increases risk of a second OCC [8]. Recent case-control designed studies aim to elucidate the beneficial effects of diets rich in fruits and vegetables in the etiology of OCC [9,10].

Early detection

- Early detection methods for OCC depend on the dentist's and primary care physician's knowledge and ability to suspect and detect early lesions in the high-risk population [11]. The evolution of diagnostic methodology includes the popularity of topical drugs, enhanced visualization, and mucosal biopsy procedures, such as toluidine blue, ViziLite (Zila, Inc., Phoenix, AZ), and brush biopsy, to allow for the detection of nonclinical abnormalities [12–15]. Controlled scientific studies may elucidate the use and application of these and other techniques in coming years. At this early stage of OCC prevention research, controversy surrounds the specific conduct of interventions. Chemoprevention using isotretinoin or β-carotene has shown promise in the treatment of patients with oral leukoplakia [16–18]. However, toxic reactions are common, and lesions may recur after therapy is discontinued. Future studies will involve microarray technologies and molecular-detection techniques for early detection and evaluation of chemopreventive drugs [4,19,20].
- A model of molecular progression of HNSCC has been uncovered by tabulating the critical genetic changes in each step of its progression [21]. The earliest and most common genetic change is the loss of chromosomal region *9p21*, resulting in the inactivation of the *p16* gene, an inhibitor of cyclin-dependent kinase, which regulates the cell cycle. One third of tumors involve the amplification of cyclin D1. When unchallenged, this oncogene activates cell cycle progression constitutively. Testing for genetic alterations may assist in identifying patients with the greatest risk of progression and lead to effective therapeutic strategies.
- Approximately 50% of HNSCC contain a mutation in the *p53* gene, which is a tumor suppressor gene that plays an important role in the arrest of cell growth from a response to DNA damage. The incidence of *p53* mutations has been shown to increase throughout the progression, from premalignant lesions to invasive carcinoma [22]. The arrest of cell growth allows for DNA repair or apoptosis. Mutations in the *p53* tumor suppressor gene may result in the accumulation of DNA damage and uncontrolled cellular growth, whereas loss of *p53* function results in the development of invasive lesions and increases the occurrence of further genetic progression [23••].

Table 1. Oral cancer staging

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor 0–2 cm in greatest dimension
T2	Tumor 2–4 cm in greatest dimension
T3	Tumor > 4 cm in greatest dimension
T4a	Tumor invades adjacent structures (*eg*, cortical bone, deep [extrinsic] muscle of tongue [genioglossus, palattoglossus, and styloglossus], maxillary sinus, and skin)
T4b	Tumor invades masticator space, pterygoid plates, or skull base, and encases internal carotid artery

(*From* Greene *et al*. [28]; with permission.)

- Vascular endothelial growth factor and hypoxia-inducible factor-1α (HIF-1α) expression have been identified as potential predictors of treatment response in patients when overexpressed [24,25]. Recent studies have shown that nuclear DNA content (ploidy) and loss of heterozygosity can be helpful in predicting the risk of OCC development in patients with premalignant lesions [26,27].
- History and physical examination remain an essential component in the staging of OCC, although the routine use of panendoscopy, radiologic studies, and other techniques to evaluate for second primary tumors remains controversial. The fine needle aspiration biopsy technique remains the standard of care for evaluation of a neck mass in patients at high risk for HNSCC. Additional information can be gained and used in staging of OCC through radiographic imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning. Recent changes in staging of OCC are important in differentiating advanced resectable cancers from tumors that are considered unresectable (Table 1) [28]. The location of palpable lymph nodes or radiographic evidence of enlarged lymph nodes should be noted by level and stage.
- Imaging modalities that are used to evaluate the oral cavity include plain radiography, nuclear medicine scintigraphy, ultrasound, CT, MRI, and PET, although CT and MRI remain the primary studies performed [29]. CT and MRI may provide a more accurate pretreatment assessment of the extent of disease and can be integrated into the pretreatment staging criteria [30–32,33•]. Panoramic radiography provides an overall view of the mandible [34], a dental evaluation, and the extent of cortical bone invasion in large tumors, although technical limitations may hinder the effectiveness of this imaging technique [35]. CT and MRI allow for differentiation of soft tissues and for assessment of the integrity of adjacent bone. MRI is used during the initial examination for tumors confined to the oral tongue or with perineural spread. CT is more sensitive for detecting small areas of cortical bone invasion, whereas MRI is better for evaluating the extent of marrow invasion by tumor. PET can be used as a functional tumor detection modality, with or without anatomic imaging (CT and MRI) [36]. PET scanning remains controversial, but indications include the evaluation of patients with nodal disease and a clinically unknown primary tumor, directing biopsies of clinically occult primary lesions, nodal staging, differentiating recurrent tumor from post-therapy changes, monitoring and predicting treatment response, and detecting secondary primary lesions and distant metastases [37,38].
- Lymph nodes at levels I, II, and III should be evaluated closely at the time of imaging. Level I and II lymph nodes should not exceed 1.5 cm in diameter, whereas other lymph nodal stations should not exceed 1 cm in diameter. It is important to evaluate the lymph nodes for the presence of necrosis

and extracapsular spread. CT is more accurate for evaluating lymph nodes for metastatic disease compared to MRI, whereas the use of PET scanning to evaluate the presence of occult metastases has not been elucidated [39].

- OCC is preceded by the presence of clinically identifiable premalignant changes of the oral mucosa. The frequency of dysplastic alterations in oral leukoplakia ranges from 15.6% to 39.2%, including approximately 3% of cases that are unsuspected squamous cell carcinoma (SCC) [40]. Leukoplakias with an intermixed red component (speckled leukoplakia or mixed leukoplakia/erythroplakia) put a patient at a greater risk for developing dysplasia (51%) or cancer (14%) [41]. In addition to cases that show invasive carcinoma when first diagnosed, 3.6% to 17.5% of noncarcinomatous leukoplakias will undergo malignant transformation in patients. In one study, 6.5% of leukoplakias with a homogeneous clinical appearance underwent malignant change; however, 23.4% of speckled leukoplakias and 36.4% of leukoplakias with microscopic evidence of dysplasia transformed into cancer in patients [42]. One study showed that 70.3% of patients with proliferative verrucous leukoplakia later developed SCC [43].
- In 65 cases of patients with oral erythroplakia, Shafer and Waldron [44] discovered that 51% of patients had invasive SCC, 40% had severe epithelial dysplasia or carcinoma in situ, and the remaining 9% exhibited mild to moderate dysplasia.
- Because all true erythroplakias show significant dysplastic changes, total surgical removal is recommended.

Surgery

- Factors identified through histopathologic studies to portend a worse prognosis include tumor thickness, tumor volume, mode of invasion, positive or close margins, lymphovascular invasion, perineural invasion, and lymphatic vessel density [45,46•,47,48,49•,50–54]. Neck lymph nodes with extracapsular extension, more than two lymph nodes involved, and invasion of adjacent structures appear to correlate with lower survival rates of patients, indicating a potential benefit of irradiation after neck dissection [45,48,55••]. Occult metastases in regional lymphatics are greater in patients with floor-of-mouth and oral tongue cancers, when the primary tumor is greater than 2 mm thick [56].
- Intraoperative frozen section assessment of mucosal and deep (oral tongue) surgical margins is recommended, with the identification of margins the greatest concern [57]. Because of soft tissue shrinkage after excision in the oral cavity, an 8- to 10-mm margin at resection is needed to obtain a pathologically clear margin of 5 mm [51]. When perineural invasion is evident, ensuring adequate margins during surgical resection may be difficult because tumor extension may be insidious and discontinuous. The negative prognostic significance of positive surgical margins in OCC is demonstrated by the doubling in the rate of local recurrence, compared to those patients with margins that were pathologically clear [58].
- Identifying tumor-positive surgical margins by histologic appearance may result in a significant source of treatment failure. Therefore, molecular staging has been introduced to HNSCC by using genetic alterations to detect rare cancer cells [23••]. Detecting *p53* mutations by polymerase chain reaction (PCR) allows for the detection of mutant cancer cells among 10,000 normal cells. Of 25 patients with negative surgical margins, 13 (52%) demonstrated the presence of neoplastic cells containing mutations after PCR analysis. At follow-up, five of the 13 patients with positive margins had biopsy-proven recurrences of carcinoma within 7 months. Another study performing similar molecular

Table 2. MUSC Hollings Cancer Center head and neck tumor program treatment guidelines for oral cavity squamous cell carcinoma

Tumor	Lip	Tongue	Floor of mouth	Hard palate	Alveolus	Retromolar trigone	Buccal mucosa	Recurrent*	Metastatic*
T1	S or RT	S	S	S	S	S	S or RT	S, RRT, or BT	C, BT
T2	S or RT	S	S or RT	S	S	S or RT	S or RT	S, BT, or RRT	C, BT
T3	S and RT	S and RT	S and RT	S and RT	S and RT	S and RT	S and RT	C, BT, S	C, BT
T4a	S and RT	S and RT (+/− C)	S and RT	S and RT	S and RT	S and RT	S and RT	C, BT, S	C, BT
T4b	C and RT	C and RT	C and RT	C and RT	C and RT	C and RT	C and RT	C, BT	C, BT

*Clinical trials.
BT—brachytherapy; C—chemotherapy; MUSC—Medical University of South Carolina; RT—radiation therapy; RRT—re-irradiation; S—surgery.

analysis revealed the *p53* mutation rate to be 72% (13 of 18) in surgical margins considered tumor free after light microscopy [59]. The technique of molecular detection will serve as an important indicator in identifying patients likely to fail treatment at the local site.

- Survival data are similar for patients with early stage OCC treated with surgery or radiation therapy, whereas patients with advanced OCC are treated best with combination therapy involving surgery and postoperative radiation therapy. Guidelines for treatment at Hollings Cancer Center tumor program are categorized in Table 2. Treatment of the primary site, neck, and reconstructive/rehabilitative techniques continues to play a critical role in the cure and functional outcome of the patient. Treatment of the neck may include a different treatment regimen than the primary site, depending on the extent of disease. A patient with N0 or N1 neck cancer, without additional risk, will have similar locoregional control with surgery or radiation therapy. A patient with N2 or N3 neck cancer may require combined surgery (neck dissection), followed by radiation therapy.
- When treating OCC, it is important to strive for complete tumor eradication, while optimizing aesthetic form and preserving aerodigestive function, including respiration, mastication, dental health, swallowing, and speech.
- Surgical resection for treatment of patients with OCC may be performed through the transoral or transcervical approach. The approach used is determined by the location of the tumor, extent of disease, treatment of the neck, and planned reconstruction.
- OCC surgery can be performed without external incisions in many stage I and stage II cancers. One- to 2-cm margins of normal-appearing tissue should be removed to ensure complete clearance of the microscopic tumor. Advanced cancers require an external or transcervical approach, in addition to neck dissection, to allow for comprehensive tumor removal, lymphadenectomy, and reconstruction. Mandibulectomy is necessary for patients with bony invasion by the tumor. The course of various nerves within the oral cavity may serve as routes for tumor spread. Cancers of the lower alveolus may track along the inferior alveolar nerve, a branch of the mandibular nerve (V3), to the skull base. The palatine nerves exiting the greater and lesser palatine foramina may serve as potential conduits of tumor infiltration from cancer of the hard palate into the pterygopalatine fossa and skull base.
- The lip requires careful evaluation of the functional outcome of patients treated with surgery or radiation therapy, which determines the best treatment for early lesions, whereas advanced lip cancer often requires combined modality treatment. Treatment of the patient's neck should be considered for involvement of the oral commissure.

- Most patients with floor-of-mouth lesions have improved locoregional control and fewer complications with surgical resection; however, patients with advanced stage cancer require adjuvant radiation. Survival rates of patients among these various treatment options are similar, depending on patient selection, and range from 83% to 93% for early lesions [60,61]. The cure rate of patients with floor-of-mouth cancer depends on the stage of the cancer, with a significant drop in survival rates of patients with advanced stage cancer.
- Most patients with tongue cancer are treated with surgical resection, with margin control and neck dissection. The tongue remains a more difficult structure to treat with radiotherapy because of the mobility, proximity to mandible and teeth, and diffuse mucosal toxicity of radiation therapy. The high rate of occult metastatic disease to the neck mandates neck dissection or neck irradiation in most cases. Patients with early cancers of the tongue (T1,T2) have approximately 60% to 80% local control rate and a lower survival rate, whereas patients with advanced stage cancers have a survival rate of less than 50% [62,63]. Zelefsky *et al.* [64] reported a 5-year local control rate of 62% in patients with stage III and IV oral tongue cancer who were treated with combined surgery and radiotherapy.

Partial glossectomy

Standard procedure	May encompass removal of a small lesion or section of the tongue, with healing by secondary intention, auto or allograft coverage, primary closure, and flap closure. It is performed for patients with T1 or T2 OCC.
Contraindications	Limited glossectomy is insufficient when the tumor extends bilaterally into the base of the tongue or into adjacent regions, such as the mandible. In these situations, a more extensive procedure would be necessary.
Complications	Dysarthria, dysphagia, dysguesia, and hypoesthesia.
Special points	At least 1-cm margin of normal tissue resection is recommended for adequate tumor removal.

Anterior composite resection

Standard procedure	This has been referred to as "jaw-neck-tongue" or "commando" procedure, and requires many modifications for tumor extirpation and reconstruction, depending on the extent of the tumor and structures involved. A portion of the patient's tongue, floor of mouth, mandible, suprahyoid musculature and adjacent nerves, arteries, and veins are included, and the procedure is indicated in patients with advanced stage III or IV OCC. Reconstruction can be performed with local tissue, primary closure, regional (pectoralis myocutaneous flap), or microvascular free flap (fibula, scapula, iliac, and radial).
Contraindications	Cosmetic deformity, dysarthria, dysphagia, drooling, trismus, malocclusion, and dysgeusia.
Complications	Wound infection, fistula, flap failure, pneumonia, and hematoma.
Special points	Patients should be educated regarding the functional and cosmetic outcome to provide for adequate perioperative rehabilitation to improve speech, swallowing, and dental/masticatory rehabilitation. Evaluation of the lingual and hypoglossal nerves and the lingual arteries and veins may predict the eventual function and viability of the remaining tongue preserved in composite partial or complete glossectomy.

Surgery of the neck

- The lymph nodes at highest risk for metastases from OCC include lymph nodes within levels I, II, and III, grouped collectively as the supraomohyoid triangle [65••]. In the 5-year survival rate of patients with HNSCC, the presence of cervical lymph node metastases decreases by 50% [66]. Aggressive management of the neck is necessary to prevent locoregional failure.

The surgical treatment of the neck has a therapeutic benefit and a diagnostic or staging benefit for patients. Surgery removes metastatic deposits in lymph nodes and lymphatic vessels within the neck, serves to determine the extent and pathologic staging, and provides prognostic evidence, such as extracapsular extension [67]. The treatment of patients with clinically positive neck cancer entails comprehensive neck dissection, with adjuvant radiotherapy. However, the treatment of patients with clinically negative neck cancer is more controversial. The risk of nodal metastases in this group approaches 25%, and elective treatment of patients with clinically negative (N0) neck cancer is warranted for lesions greater than 2 mm in depth. Elective neck dissection performed on patients with an N0 neck cancer improves rates of locoregional control [68•,69]. The most common neck dissection performed on patients with early OCC (N0) is the supraomohyoid neck dissection (SOHND), which removes levels I, II, and III lymph nodes [70]. Although the risk of "skip metastases" in level IV lymph nodes is a possible limitation of SOHND, the risk of isolated level IV lymph node involvement in the absence of other cervical nodal metastases is low, indicating that level IV lymph nodes may not require removal when there is no evidence of regional metastases in other levels [71•,72].

- The types of neck dissection include selective neck dissection (SND), modified radical neck dissection (MRND), radical neck dissection (RND), and extended radical neck dissection. SND and MRND have replaced RND in many cases [73••]. The classification is based on the levels of the lymph nodes removed and the structures requiring removal involving the lymph nodes (internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve).
- The location of the primary tumor influences the rate of metastasis to regional lymph nodes. SCC of the alveolar ridge and hard palate is less likely to metastasize to cervical lymph nodes than are primary tumors from midline structures of the oral cavity, such as the floor of the mouth or midline oral tongue, where there is increased risk for contralateral or bilateral nodal metastases [74,75].
- In the evolution toward more selective neck dissection, the applicability of sentinel lymph node biopsy, clinically useful for treating patients with cutaneous melanoma, has been investigated for treating patients with OCC [76]. However, the ability to detect metastases reliably has not been established. The associated morbidity of the procedure may not be different from that of SOHND.
- The high propensity of regional lymph node metastases in patients with primary OCC may warrant elective treatment of N0 neck cancer in most instances, excluding early lesions or primary tumors of certain anatomic sites (alveolar ridge or hard palate).

Radiation therapy

- The use of external beam radiation therapy (EBRT), with or without brachytherapy, has provided patients with OCC with an alternative to surgical treatment. EBRT has similar cure rates of patients in early stages, although complications may limit its use in early tongue cancers and other subsites of the oral cavity [77]. Studies have shown a survival benefit for patients receiving hyperfractionated and accelerated fractionated radiotherapy for HNSCC, although these techniques do not seem to have reached widespread acceptance [78••,79]. Most of the recent evidence using radiation therapy in treating HNSCC surrounds the combined usage of chemotherapy with radiation therapy for patients with advanced HNSCC, although these studies were not evaluating OCC alone [80,81••,82]. The timing of

radiation therapy, dosage, and the avoidance of breaks during treatment appear to be related to locoregional control and survival rates of patients [55••]. The use of brachytherapy in treating patients with OCC depends on the institution because these techniques require additional training and expertise, although local control may be improved with its use in close or positive margins [83]. There has been an increasing use of intensity-modulated radiation therapy (IMRT) in many tumors, including HNSCC. Although studies suggest a potential benefit for patients through reduction in toxicity, long-term survival, locoregional recurrence, and functional outcomes using IMRT have not been determined [84•].

- Salivation, mucositis, and xerostomia remain important factors in the treatment planning and medical management of patients with complications related to radiation. Studies have revealed a potential benefit from various drugs in patients during and after radiation treatment. In addition, future studies may determine the indications for drugs in combined chemotherapy and radiation therapy [85••,86].
- Several studies have addressed some of the various OCC subsites using radiation therapy. Petrovich *et al.* [87] reported on 250 patients with lip carcinoma treated with radiation therapy. The local control rate of the patients was 94% for stage I and II disease, 90% for stage III, and 47% for stage IV.
- Floor-of-mouth cancers that are not in close proximity to the mandible and extend into the ventral surface of oral tongue may be treated by surgery, brachytherapy alone, or in combination with EBRT. Radiation techniques for floor-of-mouth subsites require special attention because of the proximity of the mandible, dentition, and submandibular glands. Mazeron *et al.* [60,88,89] reported on 79 patients with floor-of-mouth cancer treated with interstitial implant alone or with EBRT. Local control rates of patients with T1 and T2 lesions was 94% and 74%, respectively. T1 tumors of the tongue may be treated by interstitial implant alone, providing local control rates of approximately 90% in patients receiving the treatment. EBRT and brachytherapy implant provide excellent local control and functional outcome in patients with T2 lesions, if most of the radiation dose is administered by the implant. Data from MD Anderson Cancer Center (Houston, TX) suggest local control rate of 92% in patients receiving less than 40 Gy EBRT and higher implant dose compared to 64% in patients receiving 40 Gy EBRT and lower implant dose for T2 oral tongue cancers [77].
- Patients receiving treatment at the primary site of the tumor should receive standard doses of radiation therapy in conventional fractions of 2 Gy, ranging from 66 to 70 Gy. Hyperfractionated regimens use 1.2-Gy twice-daily (6-hour interfraction interval) doses to a total of 81.6 Gy. Accelerated fractionation schemas include concomitant boost in the last 12 treatment days, with a 1.5-Gy dose administered as a second treatment fraction (6-hour interfraction interval) to the gross tumor. A patient with an undissected N0 neck tumor is administered 50 Gy, whereas a patient with a dissected neck tumor is administered 56 Gy and higher, depending on the pathologic specimen. Postoperative radiation dose ranges from 56 to 66 Gy, depending on risk factors, with gross residual disease receiving up to 70 Gy. Concurrent chemoradiation schedules use conventional daily fractions of 1.8 to 2 Gy.
- Treatment breaks for patients or delay of greater than 4 weeks after surgery should be discouraged. Total treatment duration in definitive radiation therapy or chemoradiation therapy should remain from 8 to 10 weeks. In the adjuvant setting, the package time from surgery to the end of radiotherapy should not exceed 12 weeks because prolongation of total treatment results in higher locoregional failure.

- Sequelae of radiotherapy depend on site of treatment, total dose, dose per fraction, time for total dose, addition of chemotherapy, volume of radiation field, proximity of tumor to critical structures, age, general physical condition of the patient, and radiation technique.
- Side effects of radiotherapy can be acute or late. The acute sequelae include lack of energy, mucositis, radiation dermatitis, taste changes, and xerostomia. Late complications include persistent mucositis, xerostomia, laryngeal edema (epiglottis and arytenoids), hypothyroidism, skin changes, hair loss, and changes in speech and deglutition. Radiation-induced secondary cancers and osteoradionecrosis of the mandible may present many years after radiotherapy, but this is rare.
- Supportive care with respect to nutrition, oral hygiene, pain medications, topical analgesic drugs, skin care, and psychologic support are important in completion of the treatment regimen.
- Pretreatment dental evaluation and extraction, fluoride prophylaxis, assessment of nutritional requirement and possible placement of a feeding tube, and smoking cessation programs are integral to the initial evaluation of radiotherapy candidates.
- Radiation fields depend on the setting of radiation therapy (definitive or adjuvant), stage and location of the primary tumor, and risk factors. Comprehensive bilateral neck irradiation and the primary tumor, with 2-cm margins, is required for patients with locally advanced carcinoma in a definitive treatment setting. Patients with early, well-lateralized tumors may be treated with ipsilateral radiation fields. In the adjuvant setting, treatment of neck cancer depends on the findings of the neck dissection. In patients with pathologically negative neck cancer, the primary site may be irradiated, depending on high-risk features. Treatment of the patient's nasal cavity, paranasal sinuses, and skull base may require specialized treatment planning.

Chemotherapy

- Systemic antineoplastic drug therapy (chemotherapy) is not a curative single modality in epithelial HNSCC, but it has an important adjunctive role. Postoperative adjuvant chemotherapy is not the standard of care for HNSCC. There is no benefit from postoperative adjuvant chemotherapy for patients who have undergone surgical resection and are at low risk for recurrence after surgery [90]. Ongoing randomized trials focus on high-risk patients, defined by the Radiation Therapy Oncology Group (positive margins of resection, two or more positive regional lymph nodes, or extracapsular extension), who have undergone surgical resection [91•].
- In other HNSCC primary sites, the use of chemotherapy with radiation therapy is promising. A large meta-analysis indicated an improved survival rate of patients with HNSCC when chemotherapy was used in the treatment regimen [92]. Sequential and concomitant chemoradiotherapy are proven alternatives to radical surgery and radiation therapy for patients with cancers of the larynx and hypopharynx and to radiation therapy for patients with oropharyngeal cancer [81••,93–95]. No trials have targeted oral cavity sites; therefore, surgery and radiation therapy remain the standards for primary therapy for patients with resectable tumors. However, chemoradiotherapy is appropriate primary therapy for patients with unresectable OCC, and is being considered as neoadjuvant therapy before definitive surgery [96•]. Based on the favorable data from other HNSCC sites, concomitant chemoradiotherapy is superior to radiation therapy alone and should be used for patients able to tolerate the additional toxicity of the combined therapy [97••,98].

- For patients with recurrent OCC, chemotherapy alone is palliative. Most regimens have used cisplatin with fluorouracil or paclitaxel; hydroxyurea, carboplatin, and docetaxel have also been used in combination with radiation therapy.
- For patients with distant metastases, especially those without prior systemic therapy, chemotherapy may be used to palliate symptoms. Combination chemotherapy regimens are more likely than single-agent methotrexate to produce objective tumor responses, but there is no evidence that they extend survival rates of patients compared to single-agent therapy [99].

Reconstruction and rehabilitation

- ONYX-015, an engineered adenovirus, was used in a recent study involving patients with recurrent HNSCC [100]. Intratumoral injection of ONYX-015, administered in combination with cisplatin and 5-fluorouracil, demonstrated improved tumor shrinkage, compared to tumors in the same patients who were not injected with the virus. Although such data are preliminary, and clinical benefit in the form of a prospective randomized trial has yet to be demonstrated, studies such as this provide unique investigation into novel modalities to improve locoregional control of patients with HNSCC.
- Masticatory function depends on the structure and neural integrity of the mandible, tongue, muscles of mastication, dentition, hard and soft palates, lips, cheeks, and adequate salivary flow, and is related to the coordinated neuromuscular interaction of the oral and pharyngeal phases of swallowing. The most significant impairments are corrected with surgery that involves the tongue and mandible, with loss of mandibular continuity [101].
- When a portion of the mandible, maxilla, or dentition must be removed during surgery or before radiation therapy, patients can be rehabilitated with a conventional tissue-borne prosthesis or an implant-retained prosthesis. Surgical reconstruction may entail the use of osteocutaneous free flaps, grafts, or other flap reconstruction, with or without osseointegrated implants.
- Marunick *et al.* [102] reported that a study evaluating masticatory function for edentulous patients showed that the extent of mandibular resection and loss of continuity decreased masticatory function. Although conventional prosthetic rehabilitation improved masticatory function for some patients, none were able to achieve pretreatment levels of masticatory function. The use of dental implants showed a significant improvement in masticatory function tests; however, there are no definitive studies regarding masticatory function in dentate patients who have lost mandibular continuity.
- There are few prospective studies that tested the functional benefit of mandibular reconstruction in patients with HNSCC, although one study evaluated patients with reconstructed mandibles who maintained mandibular continuity, patients with no reconstruction, and a control group [103]. The study revealed that patients with reconstructed mandibles had improved bite-force levels, masticatory performance levels, and vertical masticatory cycle. Additional prospective studies are needed to define the dental, masticatory, and oral function after patients receive treatment for OCC.
- Clinical experience, case reports, and cross-sectional studies show that disorders of articulation, resonance, and swallowing are common morbidities associated with oncologic treatments (*ie*, surgery, radiation, chemotherapy, or combined modalities) for patients with OCC [104–109]. The severity of the speech and swallowing impairment for patients treated with surgery for OCC depends on the size of the lesion, extent of the resection, and type of reconstruction [104–108]. The associated functional impacts of

the cancer treatments may result from local or systemic effects, such as restriction in range of structures secondary to fibrosis or tethering of tissue, xerostomia, and mucositis, that interfere with the efficiency and comfort of speech production and swallowing. There appears to be functional interdependence between structural movements and sensory enervation of the oral cavity and initiation and progression of the pharyngeal mechanics of normal swallowing [110]. Although pharyngeal and laryngeal structures involved in airway closure and pharyngeal clearance during swallowing are not included in the surgical resection or radiation field, they may be disrupted because of functional interdependence. Because of speech and swallowing impairment related to patients receiving treatment for OCC, pretreatment counseling is essential to prepare patients and families for the potential post-treatment functional morbidities, to ease their fear in the acute phase of their recovery, and to assist them with making informed decisions regarding their post-treatment rehabilitative course. However, there are few studies that provide sufficient evidence for differences between various cancer treatment modalities, such as the presence, type, and severity of speech or swallowing impairment. Furthermore, there is little evidence regarding the impact of various cancer treatment modalities on the effectiveness of speech and swallowing therapies directed toward recovery of function.

Emerging therapies

- Experimental techniques include the use of sentinel node biopsy for patients with early OCC to delineate the presence of regional metastatic disease in patients with N0 neck cancer. Several small series reveal some success with this technique, and clinical trials will determine its use in treating mucosal malignancies [111•].
- A variety of novel agents are in development, including targeted therapies that affect apoptosis, cell-cycle regulation, gene transcription, transmembrane or intracellular signal transduction, angiogenesis, and invasion [23••]. Most of the agents have demonstrated modest response rates in patients, but they have novel mechanisms of action, enhance the antineoplastic activity of traditional chemotherapeutic drugs and radiation, and have toxicity profiles that are different from traditional therapies [112]. They can be used in conjunction with chemotherapy and radiation.
- The role of gene therapy and viral therapy techniques is emerging. In one study, patients with incurable HNSCC received Ad-*p53* by intratumoral injection. Two patients showed objective tumor regression of greater than 50%, six patients showed stable disease for up to 3.5 months, and nine patients showed progressive disease [113]. Further investigation is needed to perfect this therapeutic strategy.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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