Oral cancer management

The word carcinoma (karkinos: "crab") is attributed to the father of medicine, Hippocrates (460-370 bc), who noticed that blood vessels around non–ulcer-forming and ulcer-forming tumors looked like the claws of a crab.

Once the initial evaluation, data collection, and staging are complete, a discussion regarding treatment is undertaken. The clinician and the patient are ultimately faced with deciding which treatment modality or combination offers not only the best chance for cure but also the best preservation of quality of life. Quality of life issues are becoming increasingly important in treatment planning. Despite media hyperbole on cancer treatment "breakthroughs," cancer treatment still falls into three basic categories: surgery, radiation, or chemotherapy, or some combination thereof. Choosing the appropriate treatment depends on many factors, including the patient's medical condition as well as the modalities available to the clinician.

Surgical management

Surgery remains the cornerstone of most treatment regimens for oral cavity cancer. Surgery offers several advantages, including the harvest of a specimen for histopathologic analysis and the possibility of removing the cancer utilizing one treatment modality in one session. Surgical resection with frozen-section analysis of the margins is advocated by most clinicians for most stage I and stage II cancers of the oral cavity. Although primary radiation to T1 and T2 lesions may offer similar disease control, the side effects of radiation to the oral environment outweigh those of surgery in most situations. In addition, given the rate of second primary cancers in the head and neck cancer patient population, it is often better to hold radiation if possible in case it is needed in the future.

The importance of obtaining clear histologic margins has been a foundation for surgical treatment of oral cavity cancer and has been supported by several studies that have demonstrated decreased survival associated with positive margins. Unfortunately, clear pathologic margins are not always an assurance of a good outcome.

Field cancerization is a concept that was proposed by Slaughter and colleagues in 1953, after they reviewed resection specimens from the oral cavity and oropharynx. They found multiple foci of cancer in 11% of specimens. Areas of dysplasia also existed distant from the primary site. Additional studies have shown that margins that are clear histologically may still have cells at the margin that demonstrate premalignant changes, and this can be associated with recurrence. An altered P53 gene (tumor suppressor protein) was identified in 52% of patients in one study, and recurrence occurred in almost half of these patients.

Studies have clearly shown a decreased local control and survival in patients with positive margins even in patients receiving adjuvant therapy. This is most likely due to the inability of radiation therapy to deal with the increased tumor cell burden in some cases of final positive margins.

It is agreed by most that surgeons should strive for clear margins, given the impact of positive margins on survival. Excision with 1–1.5 cm of normal tissue beyond the obvious tumor edge is generally sufficient.

Thin specimens of the margins should then be harvested from either the specimen or the wound resection periphery depending on the surgeon's preference. These thin strips are oriented for the pathologist using a specimen map. Mucosal margins as well as deep margin specimens are submitted; however, frozen-section analysis is helpful but not infallible. The role of frozen analysis of margins in oral cavity cancer has been heavily debated and its cost-effectiveness has been called into question, leading some surgeons to abandon the practice. Although frozen-section analysis is highly accurate and has a high correlation with final histologic analysis of the submitted tissue samples, its ability to predict whether the entire tumor surface of the final specimen will be clear of close or involved margins is not as reliable. For this reason, frozen sections appear to be more beneficial in smaller localized tumors.

Recent reports illustrate that pathologic margins that are positive on final analysis are more likely a reflection of the aggressiveness of the particular cancer than a reflection on the surgical procedure, and histologic risk assessment is more predictive for disease free interval (DFI) and survival than margin status.

Some authors found that final positive margins had a high correlation with aggressive histologic parameters such as perineural and lymphovascular invasion. Thus, the biologic aggressiveness suggested by positive margins may in itself account for the poorer outcome of patients with positive surgical margins and be an indication for multimodality therapy instead of attempts at re-excision. Indeed, one of the main advantages of surgery as the initial treatment modality for oral cancer is the ability to obtain a specimen to examine for known indicators of biologic aggressiveness—histologic grade, lymphovascular and perineural invasion, lack of inflammatory front at the tumor–host interface, and use these as a guide to the need for adjuvant therapy. In addition, whereas clinicians and patients are often comforted by a report of "clear margins," it must be understood that pathologic analysis at the light microscopy level is not 100% accurate and a certain number of false negatives invariably occur. This can be especially true with regards to tissue after multimodality therapy.

Radiotherapy

Cell death can be divided into two types**: reproductive cell death**, which results from damage to cellular genetic material, and **apoptosis**, which is programmed cell death. Reproductive cell death can occur as a result of single DNA strand breaks, which are common and easier for the cell to repair, or double-strand breaks, which are more difficult for the cell to recover from. Apoptosis occurs when a cell enters a programmed cell death mode as a result of damage. Radiation can cause either type of cell death and also slows cellular division.

Radiotherapy is primarily given by external beam using electromagnetic radiation or particulate components. X-rays and gamma rays represent photons. X-rays are produced by a man-made source and gamma rays are produced by radioactive decay, most commonly of cobalt 60. Particulate (particle) radiation using electrons plays an important role in head and neck cancer. Another form of particulate radiation is neutron radiotherapy, which may have a specific role in salivary gland malignancy.

Regardless of the source, radiation interacts with tissue to produce several types of damage to cells. The radiation particle-cell interaction may be either direct, or

more commonly indirect, whereby impact with H2O molecules creates secondary particles that interact with cellular DNA. The absorbed dosage unit of radiation energy is reported as a gray (Gy), which is 1 joule of absorbed dose per kilogram. Previously, the dosage unit was reported as a rad. One gray is equal to 100 rad and 1 centigray (cGy) equals 1 rad (1 cGy = 1 rad).

Some important definitions regarding radiotherapy:

- **Fractionation** refers to schedule on which radiation dose is administered. Standard radiotherapy is administered daily, 5 days a week, with weekends off. In an effort to maximize damage to the more rapidly dividing tumor cells while sparing normal tissues as much as possible, fractionation schedules have been altered.
- **Accelerated fractionation** refers to overall reduction in treatment time accomplished by giving two or more daily-dose fractions of close to conventional size each day.
- **Hyperfractionation** implies overall treatment time is conventional or slightly reduced, but an increase in total dose is achieved by giving two or more small-dose fractions on each treatment day.
- **Conformal radiation treatment** refers to more localized delivery of radiation to suspect site.
- **Intensity-modulated radiotherapy (IMRT**) is example of conformal treatment plan combined with varying radiation doses frequently used for head and neck patients to limit collateral damage to surrounding areas.
- **Brachytherapy or interstitial radiotherapy** is administered by placing radioactive source, typically radium (226Ra) or iridium (192Ir), directly into tumor mass using needles or loop catheters, whereby radiation is delivered continuously.

Radiation can be administered with curative intent in the preoperative setting or as an attempt to shrink a tumor presurgically (neoadjunct). When the primary tumor is to be treated with radiation, the clinician must also consider elective radiation of the neck for control of occult metastases.

Early-stage oral cavity cancer (T1 or T2) responds equally well to radiation or surgery. The morbidity of radiation and the inability to use it again in the case of a second primary cancer or recurrent disease make surgery a more attractive modality in most situations. Larger tumors (T3 and T4) generally respond poorly to radiation alone.

The primary role for radiation in oral cavity cancer is in the postoperative setting when there is potential for persistent disease. Postoperative radiation treatment allows easier surgery and better healing in tissues not disturbed by radiation induced fibrosis. Frozen-section analysis of margins is easier in this setting, and surgery allows improved treatment planning based on final pathology. Postoperative radiation therapy remains the mainstay in most cases of resectable cancers of the oral cavity. Improved outcomes have been reported when postoperative radiation begins within 6 weeks and ends within 100 days of surgery for oral cavity squamous cancers.

Indications for Postoperative Radiation Therapy

- Two or more lymph nodes containing metastatic disease in a neck dissection.
- Extracapsular extension (ECE) of cancer beyond the confines of a node.
- Poor histologic factors: extensive perineural or perivascular invasion, positive (close) soft tissue margins.
- Large (T3 or T4) primary cancers.

Chemotherapy

Chemotherapeutic agents kill a constant fraction of cancer cells, leaving behind a certain amount of resistant cells. These resistant cells subsequently divide and the tumor mass once again increases. Principles of chemotherapy have been developed to overcome the development of resistant cell lines such as the use of multiple agents that have demonstrated independent activity against the cancer type, the combination of drugs with differing toxicities to allow maximum dosing of each agent, and the maintenance of short intervals between dosing agents while allowing adequate recovery of normal tissues.

Because chemotherapeutic agents are most effective against cells undergoing replication, smaller and faster-growing tumors are more susceptible.

Some important definitions regarding chemotherapy:

- **Palliative chemotherapy** is given to patients with incurable disease to temporarily reduce tumor volume in the hope of improving quality of life and lengthening survival.
- **Adjuvant chemotherapy** is given to patients who have undergone treatment of their primary cancer site with surgery and/or radiation. Goals of treatment include elimination of occult disease, especially distant metastases.
- **Neoadjuvant chemotherapy** (also known as induction chemotherapy) is given to patients before definitive treatment of the primary cancer site. This tactic is generally chosen in an attempt to decrease the size of the primary cancer to make definitive treatment possible. For example, a large tumor deemed unresectable may be "downstaged" by neoadjuvant chemotherapy that shrinks it to resectable proportions, although the actual stage itself does not change.

In general, chemotherapeutic agents can be divided into cell cycle–specific and non-cell-cycle-specific agents, depending on whether the particular agent requires that the target cell be in a certain phase (G0, S, G1, or mitosis) to be effective. Agents can also be categorized based on their principle mode of action. Antimetabolites, such as methotrexate and 5-fluorouracil (5-FU), block development of certain metabolites critical for cell metabolism (frequently used in the treatment of head and neck squamous cell carcinoma). Cisplatin and carboplatin are alkylating agents that form cross-links in DNA and arrest cell division. Cisplatin is more effective in squamous cell cancer but is associated with more renal and neurologic side effects than carboplatin.

<u>Key points for the use of chemotherapy in oral cancer</u>

- To date, induction chemotherapy followed by surgery has not shown survival benefit in oral cavity cancer.

- Postoperative chemotherapy should be reserved for cases of extracapsular extension and/or positive resection margins in patients who can tolerate it.
- In patients with unresectable disease, chemotherapy is combined with radiation treatment.
- At this time, the clearest indication for chemotherapy in oral cancer is in metastatic and recurrent disease.

Examples of Special Treatment Considerations by Site

SCC of the Tongue

The oral tongue, or anterior two-thirds, is the most common subsite of origin for squamous cell carcinoma in the oral cavity which typically presents as a painless indurated ulceration. If pain is present, it is usually due to secondary infection.The tongue is considered a high-risk subsite for OSCC owing to the propensity for regional nodal metastasis through a rich lymphatic network and to a low resistance to tumor ingress and metastasis by an ill-equipped muscular composition.

As previously stated, the primary, definitive management of OSCC of the tongue with curative intent is surgery alone or with adjuvant radiation or chemo-RT, as indicated by pathologic staging.

Reconstructive options after tongue resection are largely dependent on the size of the defect after ablation, the overall functional status of the patient, the anticipated need for adjuvant treatment modalities, and the hopes of preserving functions of the tongue, including speech, mastication, and deglutition. From a reconstructive standpoint, small defects of the tongue can be easily managed with primary closure; moderate-sized defects with skin grafts or biologic dressings; and large partial glossectomies, hemiglossectomies, and subtotal or total glossectomies are most ideally managed by locoregional flaps (ie, facial artery myomucosal flap and submental island flap) or free tissue transfers (ie, radial forearm free flap, anterolateral thigh flap) and mandibulotomy may be needed for adequate access to large or posterior lesions..

The management of early-stage T1-T2 OSCC of the tongue with a clinically negative neck (cN0 neck) has remained a controversial topic within the field of

oncologic surgery. Given the propensity of occult metastasis for OSCC of the tongue at presentation, many surgeons recommend elective neck dissection (END) even for early T-staged cancers with the benefit of prognostic information from identifying pathologic regional nodal disease at the time of surgery.

Despite some variability in the recommendations of surgeons for END in early T-staged cN0 tongue cancers, evidence suggests that a large portion recommend END for patients with primary tumors of cT2 tongue stage or greater.

It is important to know that up to 10–12% of tongue cancers with metastases to the neck can demonstrate "skip" metastases to level IV, and consideration should be given to extending the neck dissection to include level IV.

SCC of the buccal mucosa

Buccal squamous cell carcinomas represent approximately 10% of oral cavity cancers in the United States compared with 41% in India. Squamous cell carcinomas of the buccal mucosa can be deceptive in their clinical course. Because of the intimacy to the buccal space and deeper structures, cancers that penetrate the buccinators muscle can be difficult to eradicate.

Patients may present with involvement of the pterygoid space posteriorly or the parotid gland laterally. Extension either superiorly or inferiorly can lead to invasion of the maxillary alveolus or mandibular alveolus, respectively. These cancers often arise in wide areas of damaged mucosa, and adequate excision of these lesions often results in complex defects of the cheek that can be difficult to reconstruct. Primary radiation may be an option for smaller lesions. Although up to 50% of patients with buccal squamous cell carcinoma can present with neck metastases, the rate of occult disease in the neck is approximately 10%.

As with other oral cancer sites, elective treatment of the neck with radiation or surgery is indicated in T3 or T4 lesions. Consideration should also be given to elective treatment of the neck in deep T1 (>4 mm) and larger T2 lesions. Combined therapy for large lesions with surgery and radiation may offer the best chance for cure.

Two-year overall survival rates for early-stage disease treated with a variety of treatment modalities range from 83% to 100%. Stage III survival rate is 41% and stage IV is 15%.

Neck dissection

The term "neck dissection" refers to a surgical procedure in which the fibrofatty contents of the neck are removed for the treatment of cervical lymphatic metastases.

Appropriate surgical management of the regional lymphatics plays a central role in the treatment of oral cancer patients. Removal of the at-risk lymphatic basins serves two important purposes: (1) to remove and identify occult metastasis in patients in whom cervical metastasis are at risk; the elective neck dissection (note should be made here that the term “prophylactic neck dissection” should be avoided and replaced with the more accurate term elective neck dissection when discussing removal of at-risk lymphatic basins in the absence of clinical evidence of metastasis); or (2) to remove macroscopic disease in patients in whom metastasis are highly suspected based on imaging, clinical examination, or biopsy via fine-needle aspiration: termed therapeutic neck dissection.

Classification of neck dissection

- **Radical neck dissection:** Refers to the removal of all ipsilateral cervical lymph node groups extending from the inferior border of the mandible to the clavicle, from the lateral border of the sternohyoid muscle, hyoid bone, and contralateral anterior belly of the digastric muscle medially to the anterior border of the trapezius. Included are levels I through V. This entails the removal of three important nonlymphatic structures— the internal jugular vein, the sternocleidomastoid muscle, and the spinal accessory nerve.
- **Modified radical neck dissection**: Refers to removal of the same lymph node levels (I–V) as the radical neck dissection, but with preservation of the spinal accessory nerve, the internal jugular vein, or the sternocleidomastoid muscle. The structures preserved should be named. Some authors propose subdividing the modified neck dissection into three types:

MRND type I is preservation of one of these structures, MRND type II is preservation of two structures and so on). Both RND and MRND are used when the neck has evidence of nodal metastasis (N+), although there is growing evidence to suggest that SND has a role to play not only in staging but also in the management of the N+ neck.

- **Selective neck dissectio**n (SND): Refers to the preservation of one or more lymph node groups normally removed in a radical neck dissection. In the 1991 classification scheme, there were several "named" selective neck dissections. For example, the supraomohyoid neck dissection removed the lymph nodes from levels I to III. The subsequent proposed modification in 2001 sought to eliminate these "named" dissections. The committee proposed that selective neck dissections be named for the cancer that the surgeon was treating and to name the node groups removed in parenthesis. For example, a selective neck dissection for oral cavity cancer would encompass those node groups most at risk (levels I–III) and be referred to as a selective neck dissection (levels I–III).
- **Extended neck dissection:** Refers to the removal of one or more additional lymph node groups, nonlymphatic structures, or both, not encompassed by a radical neck dissection. For example, mediastinal nodes or nonlymphatic structures such as the carotid artery or hypoglossal nerve.

For an oral cavity primary without evidence of lymph node metastases, a selective neck dissection removing lymph nodes from levels I to III is the generally accepted procedure. Shah and associates demonstrated supraomohyoid neck dissection to eradicate occult metastatic disease in 95% of patients. Some surgeons, however, advocate including level IV (extended supraomohyoid neck dissection) to decrease the risk, however small, of missed occult metastases.

Modifications of neck dissections have been made in an attempt to prevent the morbidity of radical neck dissection. Preservation of the spinal accessory nerve decreases the incidence of painful shoulder syndrome.