

Chapter II

CURRENT THERAPIES AND FUTURE TREATMENT MODALITIES FOR ORAL CAVITY CANCER

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ABSTRACT

Oral cancer is an increasingly prevalent disease in the United States. Although it accounts for only about 3% of all malignancies in this country, it encompasses approximately 30 percent of all head and neck neoplasms. It is estimated that 34,360 Americans will be diagnosed with oral cancer in 2007 and of these, 7,550 individuals will eventually succumb to their disease. Despite recent advances in surgery, radiation, chemotherapy, and the shift toward multi-modality treatment, the overall 5-year survival rates have not improved from the 1970s (50-55%).

Oral cancers often begin as premalignant lesions, such as leukoplakia, erythroplakia, and, less commonly, lichen planus. Because clinical evidence of such lesions may be visible with a thorough physical exam, dentists, oral surgeons and otolaryngologists all play an integral role in early detection and prevention of cancers of the oral cavity. Ongoing technological advances have facilitated radiological detection of primary tumors and surveillance for the early detection of recurrences. While computed tomography (CT) and magnetic resonant imaging (MRI) have become the mainstay imaging tools for surgeons, the widespread availability of positron emission tomography (PET) has allowed for whole body surveillance where applicable, and has brought new hope for cancer detection. On the surgical front, the utility of sentinel lymph node biopsy (SLNB) for staging malignant melanoma and breast cancer has served as an impetus for its early experimental use as a potential procedure of choice for staging oral cavity cancers.

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However, the effectiveness of SLNB for oral cancer staging has yet to be proven. While radiation therapy continues to evolve in its precision in the treatment of oral cavity cancers, chemotherapy adjuncts have remained largely unchanged in the agents administered, but the duration and timing of chemotherapy regimes continues to be investigated and evolving. One of the main drawbacks from the use of radiation therapy, and to a lesser extent, chemotherapy are the unique treatment-related sequelae of the oral cavity.

In this chapter, we will review current practices and investigate some future directions for the diagnosis and treatment of oral cancers.

INTRODUCTION

Squamous cell carcinoma, by far, is the most common cancer of the oral cavity. In fact, it is the sixth most common malignancy worldwide [1,2]. It accounts for 4% of all cancers and 2% of all cancer-related deaths worldwide each year [3]. In some of the areas of the world, the prevalence of oral cavity cancer is even more significant, as evidenced in India, where this disease process is the most common malignancy, accounting for 30% to 50% of all cancers [4,5].

This is a disease of older individuals, with the mean age at diagnosis of 60 years of age [6-8]. This fact is realized once one understands that the incidence in patients younger than forty years of age ranges between 0.4% and 4% [9]. At the turn of the century, a very strong male predilection was seen, however, now, the incidence rates for both men and women are nearly equal, as the rate of tobacco use has equalized between the sexes. The rate of a second primary, *ie* synchronous, tumor in the upper aerodigestive tract is 3.7% per year [10,11].

Of all of the prognostic factors, the cervical lymph node status, is the single most important factor in determining a patient's overall survival. In fact, the presence of regional metastasis to the cervical lymph nodes reduces the 5-year survival rate by 50% [12-14]. The primary treatment of oral cavity cancer is via surgical resection, with adjuvant chemoradiation therapy reserved for more advanced stage disease, nonresectable disease, patients with distant metastatic disease, or patients with significant comorbidities that would preclude surgery. Despite advances in surgical and adjuvant chemoradiation therapy, the diagnosis of oral cavity cancer continues to portend a poor prognosis. This is evidenced by the fact that the overall 5-year survival rate has remained essentially unchanged, at approximately 50%, over the past 30 years [12,15]. The aggressiveness of this disease is emphasized by the fact that the recurrence rate ranges from 25% to 48% despite adequate local control [16-18].

Since the 5-year survival rate for oral cavity cancer is directly related to the stage at the time of diagnosis, prevention and early detection are vital to decreasing the incidence and improving the overall survival rates of individuals diagnosed with this disease. It is important to understand that oral premalignant lesions and early stage malignancies often arise as subtle lesions. A physician should always have a high index of suspicion for any abnormality that presents in the oral cavity of a patient, especially if any risk factors are present.

Invasive squamous cell carcinoma of the oral cavity is often preceded by the presence of a clinically detectable premalignant lesion on the oral mucosa. This is defined as morphologically altered tissue in which cancer is more likely to occur than in its normal counterpart [19]. These lesions frequently present as either a white or red lesion, and as they progress, may ulcerate. It is important to note that even at this stage, these lesions are still normally asymptomatic.

Primary oral cavity lesions are normally noted by the patient, their dentist, or their physician as an ulcer or mass. 90% of all oral cavity lesions arise from three sites: the floor of mouth, the ventrolateral aspect of the tongue, and the soft palate [20]. Therefore, a focused exam in these areas is of the utmost importance. The importance of this is understood once one realizes that it has been estimated that only approximately 20% of Americans receives a thorough, focused oral cavity examination regularly [21].

INITIAL EVALUATION

All patients should be evaluated beginning with a complete history and physical examination, including a thorough exam of the head, neck, and the oral cavity. All mucosal surfaces, skin, scalp, tongue, hard and soft palate, dentition, cervical nodes, and the cranial nerves should be examined. Characteristics of any suspicious lesions should be carefully noted. These include size, appearance, location, texture, color, and fixation to adjacent structures. Some telltale signs of malignancy consist of otalgia, dysphagia, odynophagia, and unexplained bleeding.

Once a suspicious lesion is identified, a simple biopsy may be performed under local anesthesia. However, some patients may require flexible fiberoptic laryngoscopy, direct laryngoscopy, and/or esophagoscopy to better visualization and determine the extent of the mass and ultimately obtain an adequate biopsy for pathological diagnosis.

PREMALIGNANT LESIONS

Oral squamous cell carcinoma is, by far, the most common type of oral cavity cancer, accounting for greater than 90% of all oral cavity cancers. The risk factors include tobacco, alcohol, and viruses. Tobacco use is well documented in multiple studies as a dose-dependent risk factor in increasing the risk of developing oral cancer. Not only does smoking increase the incidence of developing a first primary carcinoma, but it also increases an individual's risk of recurrence, as well as, developing a second primary carcinoma by as much as 40% [22]. Excessive alcohol consumption, in addition to tobacco use, has been shown to have a synergistic effect in terms of acquiring an oral cavity tumor. One study quotes as much as a 2.5 fold risk increase over the additive risk of these two habits [23]. Evidence suggests human papilloma virus (HPV) may be a precursor in the development of some oral cancers. This is based in the discovery of HPV isolates in both oral squamous cell carcinoma and premalignant lesions of the oral cavity [24].

The 5-year survival rate for oral cancer is directly related to the stage of the disease at the time of diagnosis [25]. Therefore, prevention and early detection of premalignant lesions are essential to improve both morbidity and mortality. A premalignant lesion is defined as any morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart [19]. Three of the most common examples of these lesions in the oral cavity include leukoplakia, erythroplakia, and lichen planus.

Leukoplakia is also known as the “white plaque” due to its physical appearance. Microscopically, it has characteristics of both hyperkeratosis and dysplasia. The rate of malignant transformation from leukoplakia to squamous cell carcinoma has been shown to increase as the percentage of epithelial dysplasia increases. In fact, some studies have quoted transformation rates as high as 39% [26]. Of interest, the rate of transformation for leukoplakia is significantly higher in nonsmokers than that of smokers. Other risk factors for malignant transformation of oral leukoplakia include female gender, longstanding lesions, lesions isolated to the floor-of-mouth and tongue subsites, inhomogeneous leukoplakia, and the presence of *Candida albicans* within the lesion [27]. Because of the high malignant potential, all lesions require biopsy. Once a diagnosis has been established, the treatment options include surgical excision, cryosurgery, and CO₂ laser excision, all of which have been shown to have similar success in effectively removing the lesion. Nonsurgical therapies, such as the use of Vitamin A and beta carotene, have also shown promise in multifocal lesions, and carry the added benefit of a more favorable side effect profile.

Oral erythroplakia is a red lesion and occurs much less commonly than leukoplakia. Almost all true erythroplakias demonstrate significant epithelial dysplasia, carcinoma *in situ*, or invasive squamous cell carcinoma at the time of diagnosis [28]. Therefore, excisional biopsies are recommended so that the specimen may be assessed microscopically for margin control.

Oral lichen planus is thought to be an immunologically induced degeneration of the basal cell layer of the mucosa [29]. It presents clinically in six histological subtypes: reticular, popular, plaque-like, atrophic, bullous, and erosive. The malignant transformation rate for lichen planus is relatively low, ranging 0.4% to 5.6%. It is important to note that the atrophic and erosive subtypes have the highest rates of malignant transformation [30]. At the present time, there is no definitive cure for lichen planus, however, either topical or systemic corticosteroids are the mainstay therapy. Observation alone is a reasonable alternative.

RADIOGRAPHIC IMAGING

Panorex represents an inexpensive readily available modality that is useful in assessing dentition. In addition, patient with gross cortical involvement will have changes noted on a panorex (Figure 1). Computed tomography (CT) is the most common imaging modality used today in the assessment of oral cavity tumors because of its ability to distinguish tumor from fat with intravenous contrast use. CT scans also visibly display bone changes, such as cortical destruction of skull base and mandible (Figures 2,3), and perineural tumor invasion (Figure 4). The recent advent of the DentaScan technology has further enhanced the anatomic details

provided by CT with better images of the mandible, maxilla, and teeth [31]. Advantages of CT include availability, lower cost, and good soft tissue discrimination.

The most significant drawback to CT imaging of the oral cavity is beam-hardening artifact attributing to dental amalgam. Due to the prevalence of such artifacts, magnetic resonant imaging (MRI) may be beneficial in the evaluation of oral cavity tumors (Figure 5). MRI has been demonstrated to be superior for delineating tumor margins because of its enhanced soft tissue contrast. In addition, MRI of the face and skull base is more sensitive than CT for evaluation of perineural tumor spread (Figure 6). This point is extremely important, because this finding automatically upgrades a tumor's status to T4. It is also important to note that perineural invasion can be a clinically silent occurrence [32]. While the properties of a MRI scan often allow superior delineation of soft tissue details compared to a CT scan, the same properties of the MRI prevent the acquisition of the same bony detail. Therefore, if bony tumor invasion is suspected or if bone resection is anticipated due to the proximity of a tumor, a CT scan with intravenous contrast should be considered to help assess bone involvement in the surgical planning stage of the patient's work-up. MR angiography is an excellent screen for carotid artery involvement by carcinoma (Figure 7).

In the last few years, positron emission tomography (PET) has emerged as an exciting new imaging modality. Detection of a tumor by PET is based on the differential uptake of the radiolabeled glucose (fluoro-deoxy-glucose or FDG) in the malignant tissues compared to the surrounding normal tissues. This is due to the increased metabolic rate of the cancer cells compared to metabolism of normal tissues. Hence, tumors will routinely tend to uptake FDG more readily than normal tissues. Two studies have already demonstrated the superiority of PET over CT or MRI in tumor surveillance and recurrence, although much more investigation is needed to verify these results on a larger scale [33,34]. Currently, PET use is limited by its availability and high cost. Although PET has already proven to be a valuable tool in tumor surveillance, it should be noted that one of the major limitations is during the early postoperative period. PET scanning may remain positive at the resection site for several months. Therefore, it is recommended that the first PET scan following a resection of an oral cavity cancer should be postponed for 12 weeks to avoid a false-positive result.

More recently, combined PET-CT scanners have allowed for the combination of the molecular contrast of PET with the anatomic precision of CT (Figure 7). In concert, they enhance the ability to distinguish abnormal from physiologic FDG uptake, and hence, enhance tumor detection. Moreover, the role of PET-CT has evolved from a cancer detection and surveillance modality to one of cancer treatment. In this capacity, it is used to direct radiation therapy. Further investigation is still warranted to determine the usefulness of PET-CT in the treatment of oral cavity cancer.

STAGING

In 1940, the French surgeon, Pierre Denoix, developed the TNM staging system for classification of malignant tumors. It is still accepted today as the gold standard for tumor staging is due to the foresight and innovative thinking of Dr. Denoix at a time when little was known about cancer principles. The system takes into account all three main components of

any malignancy. The first parameter, T, is determined by the surface diameter of the primary tumor. The second parameter, N, is based not only on the presence or absence of regional lymph node metastasis, but also on the actual size of the affected node. While N is based on the regional or cervical lymph node status, M, indicates either the presence or absence of distant metastasis. Table 1 details the TNM staging system for oral cancer [35]. The TNM classification of a patient is the basis of determining the overall stage of a patient. In 1959, the American Joint Committee on Cancer (AJCC) used the basic premise of a patient's TNM classification as the basis of determining the overall stage of a patient's tumor burden. The AJCC published the first edition of the Manual for Staging of Cancer in 1977, and every few years, a new edition is published with updates and new schemes for additional cancer sites. In Table 2, the most recent AJCC staging system for oral cavity malignancies is outlined [36].

Table 1. TNM staging system for tumors of oral cavity

Tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor \leq 2cm in greatest dimension
T2	Tumor $>$ 2cm but $<$ 4cm in greatest dimension
T3	Tumor $>$ 4cm in greatest dimension
T4a	Tumor invades through cortical bone, into deep tongue musculature, maxillary sinus, or skin of face
T4b	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Node	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single ipsilateral lymph node, \leq 3cm in greatest dimension
N2a	Single ipsilateral lymph node $>$ 3cm but $<$ 6cm in greatest dimension
N2b	Multiple ipsilateral lymph nodes, non $>$ 6cm in greatest dimension
N2c	Bilateral or contralateral lymph nodes, non $>$ 6cm in greatest dimension
N3	Any lymph node $>$ 6cm in greatest dimension
Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

SURGICAL MANAGEMENT OF THE NECK

Although there are many various factors that will adversely influence the overall survival of a patient diagnosed with oral cavity squamous cell carcinoma, cervical lymph node metastasis has been shown to be the single most reliable prognostic factor in determining the outcome of an individual with this disease. In patients with cervical metastasis at the time of diagnosis, the 5-year overall survival rate is reduced by approximately 50% [37,38].

Therefore, an oncologically sound surgical removal of the cervical lymph nodes and detection of occult nodal metastasis are crucial in the comprehensive management of squamous cell carcinoma of the oral cavity. Occult neck disease is defined as disease that is present microscopically but cannot be palpated clinically and may defy identification by any of the various imaging modalities. These patients are staged as N0 on the basis of their clinical examination and pN+ if pathologically positive nodes are discovered after the neck dissection has been evaluated by the Pathologist. Salvage rates for these patients are unfavorable, and thus, elective surgical removal of the cervical lymph nodes should be executed liberally with curative intent [39].

Table 2. AJCC stage groupings

Stage group	T stage	N stage	M stage
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IV A	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IV B	T4b	Any N	M0
	Any T	N3	M0
IV C	Any T	Any N	M1

Each side of the neck is divided into various levels, and the delineation of each of the levels is explained in Table 3. While each of the levels of the neck have an anatomical basis, they also correlate to the specific regions of the neck that each head and neck primary cancer is most prone to metastasize to in the neck. Therefore, the origin of the primary tumor will determine which type of neck dissection should be performed. Table 4 explains each of the various neck dissections that are routinely performed [40,41].

In oral cavity carcinoma patients with a clinically N0 neck, the first echelon nodes that must be addressed are present in levels I, II, and III. Because a supraomohyoid neck dissection, by definition, removes lymph node levels I-III while preserving the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle, it is the best modality for detecting cervical metastasis [42-46]. The supraomohyoid neck dissection has an estimated accuracy in detection of regional metastasis of 98%, a sensitivity of 95%, and specificity of 100% [47]. This selective approach reduces morbidity compared with that of the more traditional modified radical neck dissection. It is now recommended to perform supraomohyoid neck dissection in all T1-T4 lesions with a clinically N0 neck [48,49].

The concept of skip metastases from oral tongue cancers beyond level 3 initially challenged the effectiveness of the supraomohyoid neck dissection. This is because Byers *et al.* showed that stage I and II squamous cell carcinoma of the tongue had a high likelihood of occult level IV metastases, and would therefore not be addressed by the procedure [50]. However, since this study, T1-T3 N0 oral tongue cancers have demonstrated a low rate of metastasis ($\leq 2\%$) to level IV. It has also been shown that when the decision is made intraoperatively to perform a level IV dissection based on the suspicion of metastatic disease in levels II or III, there is no increase in the rate of recurrence in the neck [51].

Table 3. Oncologic lymph node levels of the neck

LN Group		Description
IA	Submental	Within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone
IB	Submandibular	Within the boundaries of the anterior belly of the digastric muscle and the stylohyoid muscle and the inferior border of the mandible
II	Upper jugular	Around the upper third of the internal jugular vein and the adjacent spinal accessory nerve
IIA		Anterior (medial) to the spinal accessory nerve
IIB		Posterior (lateral) to the spinal accessory nerve
III	Middle jugular	Around the middle third of the internal jugular vein, between the inferior border of the hyoid bone and the inferior border of the cricoid cartilage
IV	Lower jugular	Around the lower third of the internal jugular vein, extend from the inferior border of the cricoid cartilage to the clavicle
V	Posterior triangle	Along the lower half of the spinal accessory nerve and the transverse cervical artery
VI	Central compartment	In the prelaryngeal, pretracheal, paratracheal, and tracheoesophageal groove, bounded by the hyoid bone to the suprasternal notch and between the medial borders of the carotid sheaths (LNs generally not dissected in oral cancer patients)
VII	Superior mediastinal	In the anterior superior mediastinum and tracheoesophageal grooves, extending from the suprasternal notch to the innominate artery (LNs generally not dissected in oral cancer patients)

When patients present with clinically palpable cervical metastasis, *i.e.* the N+ neck, levels I-IV are all at high risk. In this situation, a type I modified radical neck dissection is warranted. In this dissection, all the lymph nodes are removed from these levels without sacrificing the spinal accessory nerve, internal jugular vein, or the sternocleidomastoid muscle, as long as these structures are not involved with the tumor. It is important to note that palpable nodes have a significantly higher incidence of extracapsular spread of disease, which in turn, compromises the aponeurotic planes that are critical in preserving the sternocleidomastoid muscle, cranial nerve XI, and internal jugular vein [52]. Postoperative radiation therapy following type I modified radical neck dissection in an N+ neck results in failure rates of 7%-10% in N1 patients, and 12% in N2 patients [53]. These outcomes are as favorable as the cure rates that result from radical neck dissections in similar patients, and carry much less morbidity due to the preservation of function of these key structures [54].

Thus, a type I modified radical neck dissection is both a safe and appropriate treatment modality in treating N+ patients with oral cavity cancers.

Table 4. Classification of neck dissections

Neck dissection	Description
Selective	
Supraomohyoid	Lymph nodes (LNs) are removed from levels I, II, and III
Anterolateral	LNs are removed from levels II, III, and IV
Posterolateral	LNs are removed from levels II, III, IV, and V
Modified	Excision of LNs from levels I-IV with the preservation of one or more nonlymphatic structures
Type I	Preservation of the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle
Type II	Preservation of the spinal accessory nerve and the internal jugular vein
Type III	Preservation of the spinal accessory nerve
Radical	Excision of LNs from levels I-IV, the spinal accessory nerve, the internal jugular vein, the sternocleidomastoid muscle, and the submandibular gland
Extended	Excision of LN groups and/or additional structures not included in the classic neck dissection

SENTINEL LYMPH NODE BIOPSY

The theory of sentinel lymph node biopsy (SLNB) relies on the concept that metastasis from a primary tumor occurs by an orderly spread to the first echelon lymph nodes before reaching nodes in the lymphatic basin. SLNB has improved the staging accuracy in melanoma and breast cancers while, at the same time, reducing the morbidity from performing unnecessary lymph node dissections. Therefore, the success of SLNB for staging malignant melanoma and breast cancer has made it the potential procedure of choice for staging oral cavity cancers [55-56]. Hence, it has been hypothesized that if applied to patients diagnosed with oral cavity cancer, this modality could limit both the extent and number of neck dissections that would be otherwise be required for local control in patients with oral cavity cancer.

The Second International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer piloted the study with contributions from twenty centers from around the world. Sentinel lymph nodes were identified in 366 out of 379 patients with N0 disease, for an identification rate of 97% [57]. Of the 366 patients with a positive sentinel lymph node, 103 (29%) were positive for occult metastasis while 263 (71%) were negative. Of the 263 patients, 11 (4%) showed nodal disease that was not revealed by the sentinel lymph node biopsy. Hence, the negative predictive value of a negative sentinel node for the remaining neck was 96% [58]. As one can ascertain, SLNB was felt to be sufficiently validated for early oral cancer with a N0 neck [59].

The original promising results of SLNB have since been validated by other studies. For example, the preliminary results of the 1998 Canniesburn trial, the largest multicenter cohort study on SLNB to date, described an identification rate of 93%. Since then, results from other centers and trials have revealed an overall identification rate of 97.7%.

Once the sentinel lymph node is successfully identified, the possibility of the presence of an occult metastasis must also be determined. This is important because it upstages the clinically N0 neck, which inversely correlates to the overall 5-year survival of patients. The rate of upstaging by SLNB was compared to elective neck dissection in the Canniesburn trial, as well as, another study. From these trials two trials, 34%-60% of patients were upstaged. This is a dramatic improvement compared to the 30% of patients where were upstaged after undergoing a traditional elective neck dissection [60]. It is generally felt that the increased rate in upstaging following sentinel lymph node biopsy may be explained by the increase in identification of micrometastases. Due to this belief, the presence of micrometastatic disease has been given the new classification pNmi, or pathologic nodal micrometastasis. The clinical significance of pNmi has yet to be confirmed, and prospective studies with uniform pathologic evaluations are still warranted to answer this very important question [61].

The accuracy of SLNB must also be validated before it can be accepted as a satisfactory alternative to the elective neck dissection. This may be accomplished by evaluating the sensitivity of sentinel lymph node biopsy, which is defined as the proportion of patients with occult metastasis who are found to have positive sentinel lymph nodes. In published reports, including the Canniesburn trial, the sensitivity of SLNB ranges from 86%-100%. In addition, the Canniesburn trial also reported a negative predictive value of 83%-99% with a 95% confidence interval. The trial also determined the likelihood ratio to be 0.09 for negative SLNB findings [58]. These results strongly suggest that sentinel lymph node biopsy has a low false-negative rate and is sensitive enough to rule out occult metastasis when the result is negative [61].

Despite its high sensitivity and accuracy comparable to that of an elective neck dissection in detecting occult metastases, SLNB must offer advantages over neck dissection in order to become the standard of care. Currently, management of patients staged by sentinel lymph node biopsy has not been compared with that of patients staged by elective neck dissection in prospective studies. Furthermore, additional challenges specific to the oral cavity such as lymphatic mapping in deeply infiltrative primary oral tumors and the phenomenon of skip metastasis from carcinoma of the tongue still need to be investigated. The American College of Surgeons Oncology Group and the European Organization for Research and Treatment of Cancer are presently each performing a trial in an attempt to further elucidate the validity of SLNB [62,63].

RADIATION THERAPY

It is generally accepted that radiation therapy and surgery are equally successful in controlling early T1 lesions of the oral cavity [64-66]. However, Carvalho and colleagues found that among 1,500 patients with T1 and T2 oral cavity cancer, the highest recurrence rate occurred after treatment by radiation therapy alone (32.8%). When compared to the

group of patients who were treated with surgery alone, the recurrence rate was decreased to 13.9% [65]. Therefore, it is clear that these results indicate that one should surgically excise any oral cavity lesions of any T2 or more advanced disease. For T1 disease, the treatment option should be determined by location of the lesion, patient's physical condition, and the experience of the treating physician. Anyone opting for radiation therapy as their treatment should be counseled that this treatment modality usually requires at least six weeks. The patient should also understand that if a cure is not obtained through radiation therapy, then surgery would have to be performed in hopes of curing the disease process. Hence, these facts may very well affect a patient's preference in which therapy they are more amenable to undergoing. Although radiation therapy does offer better functional results, such as, superior speech and swallowing, it also carries substantial side effects. The most common include diminution of taste, xerostomia, and osteoradionecrosis of the mandible. It should be noted that newer technologies, such as intensity-modulated radiation therapy (IMRT), are overcoming some of these challenges through more focused targeting [67] (Figure 9).

For patients with T3 and T4 oral cavity cancer, combined therapy with surgery and postoperative radiation therapy is the standard of care [68]. On the other hand, preoperative radiation therapy has not provided any advantages one would expect. This was concluded from the first and only large randomized trial comparing preoperative and postoperative radiation treatments, which revealed no significant difference between overall survival, disease-free survival, and surgical complications [69]. Robotic radiosurgery as sole treatment of recurrences or given as a boost with primary radiation therapy may play a substantial role in future organ preservation protocols (Figure 9).

CHEMOTHERAPY

In the early 1980s, locally advanced head and neck cancer was found to have a high response rate to induction chemotherapy [70]. Naturally, there was great hope that induction chemotherapy would be of benefit before surgical resection for advanced disease by reducing the tumor burden to such an extent that important structures could be spared in the resection due to the response to the induction chemotherapy, and thereby causing less morbidity to the patient. Unfortunately, the initial enthusiasm failed to produce any statistically significant survival advantage. In the same regard, the recent Radiation Therapy Oncology Group (RTOG) trial reported no improvement in survival for adjuvant chemotherapy after surgical resection of head and neck cancer [71]. A number of reasons have been postulated for the relative ineffectiveness of chemotherapy in head and neck cancer. These include low growth fractions in squamous cell carcinomas, insensitivity of squamous cells to chemotherapeutic agents, decreased vascularity to tumor bed secondary to surgery or radiation, and poor patient compliance or tolerance to chemotherapy toxicities [72,73].

Optimism for the role of chemotherapy in the treatment of stage III and IV oral cavity cancer rose again when it was realized that combining chemotherapy with postoperative radiation therapy improved both local regional control, as well as, overall survival. The theory behind these observations is that chemotherapy agents can enhance radiation efficacy by the mechanism of radiosensitization. Hypotheses for this phenomenon favor the belief that

chemotherapy may alter the repair of sublethal cell damage, alter the cell cycle kinetics to favor G2/M arrest, and eliminate clonogens responsible for accelerated repopulation. All of these effects would augment the effectiveness of postoperative radiation therapy [74].

There are now several phase III trials supporting the use of concomitant chemotherapy with postoperative radiation therapy over radiation alone in terms of progression-free, disease-free, relapse-free, and overall survival. From the results of these studies, it is recommended that patients who have unresectable disease, as well as those who are at high risk for recurrence, should be strongly considered for concurrent chemoradiation therapy [71,75-87].

RECURRENCE

Recurrence rates for oral squamous cell carcinoma have been reported to be as high as 25-48% despite a sound, oncologic primary resection and treatment of cervical lymph nodes [16,17,88]. Because recurrent cancer most likely occurs at the primary site within the first 24 to 36 months, close follow-up for tumor surveillance is critical. Regularly scheduled imaging with CT, MRI, and PET scan are all important modalities used for tumor surveillance. Physical examination is also very important in this regard. Patients should understand that abstinence from tobacco and alcohol is paramount in an attempt to minimize the risk of developing a second primary lesion.

It has been found that the time interval between the completion of treatment and the local recurrence is critical in determining the overall prognosis and salvageability of the patient. Schwartz *et al* reported that recurrences that occurred within the first 6 months of primary tumor treatment resulted in an average of a 20 month survival time with no overall survivors. On the other hand, recurrences that occurred later than 6 months after initial treatment had a 58 month mean survival time, and 21% of the patients were ultimately salvaged through surgery [89].

Interestingly, several studies have found no correlation between the stage of the recurrence and the survival time. Instead, the stage and histologic grade of the primary tumor were more important in predicting the overall survival time and salvageability [90,91]. Distant recurrence after initial treatment in oral cavity cancer is associated with a very poor prognosis. In fact, these patients have a mean survival time of 4 to 12 months. Although maintenance chemotherapy may be of benefit in these cases, most patients die from local regional failure and other comorbid medical conditions [92].

Among all of the oral cavity cancer patients who present with a recurrence, about half are considered not salvageable through surgery because of the advanced stage of the tumor at presentation, involvement of local vital structures, distant metastatic disease, and poor surgical risk [45,93-95].

It is important to note that the initial treatment a patient receives for the primary tumor is important in determining the options ultimately available for salvage. For instance, location of the recurrence in relation to vital structures, previous reconstructions, and previous adjuvant chemoradiation therapies all need to be considered in evaluation for salvage

therapy. Ultimately, surgeons must determine whether salvage surgery for recurrent oral cavity cancer is justified for each patient on an individual basis.

CONCLUSION

As evidenced from this chapter, oral cavity cancer remains an aggressive disease. Although the advent of technology has brought about many advances in both the diagnosis and treatment of this disease, we still have a long road ahead in an attempt to reduce both the morbidity of treatment and the overall mortality.

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