Review

Current Management of Advanced Resectable Oral Cavity Squamous Cell Carcinoma

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The oral cavity is the most common site of head and neck squamous cell carcinoma, a disease which results in significant morbidity and mortality worldwide. Though the primary modality of treatment for patients with oral cavity cancer remains surgical resection, many patients present with advanced disease and are thus treated using a multi-disciplinary approach. Patients with extracapsular spread of lymphatic metastasis and surgical margins that remain positive have been found to be at high risk for local-regional recurrence and death from disease, and are most often recommended to receive both post-operative radiation as well as systemic chemotherapy. The basis for this approach, as well as scientific developments that underly future trials of novels treatments for patients with high-risk oral cavity cancer are reviewed.

Key Words: Oral cancer, Head and neck neoplasms, Treatment, Surgery, Radiotherapy, Chemotherapy

INTRODUCTION

It is estimated that 24,000 patients are diagnosed with oral cavity squamous cell carcinoma (OCSCC) in the United States each year (1), and oral cavity cancer ranks among the top ten most prevalent malignancies affecting patients worldwide (2). Squamous cell carcinoma is by far the most common histology found for tumors of the oral cavity. Oral subsites that may be the locus for primary tumors include the oral tongue, floor of mouth, retromolar trigone, upper and lower gingiva, hard palate, buccal mucosa, and the oral lips. Advanced local disease and lymph node metastasis are associated with poor prognosis, which is reflected in the current AJCC staging system (3). Lymph node metastases are present in approximately 45% of patients diagnosed with OCSCC (4, 5), and the presence of lymph node disease decreases patient survival by approximately 50% (6-8).

The treatment of advanced-stage oral cavity carcinoma currently involves a mutli-disciplinary team approach led by the head and neck surgeon, radiation oncologist, and medical oncologist. The mainstay of treatment for these patients is surgical resection, neck dissection, and postoperative radiation treatment directed at the primary site of disease and the draining nodal basins in the neck. However, in 2004, two large prospective randomized trials evaluating patients with advanced, resectable head and neck squamous cell carcinomas (HNSCC) identified patients with extracapsular spread of cervical lymph node disease or surgical margins positive for tumor as prognostic factors that increased the risk for poor outcome (9-11). The addition of concurrent chemotherapy to postoperative radiation treatment was found to improve outcomes for this high-risk patient population. Here we provide a detailed review of the contemporary management for patients with advanced oral cavity cancer.

DIAGNOSIS AND STAGING

The most common risk factors for the development of oral cavity cancer are the use of tobacco and alcohol. Heavy cigarette use is associated with a three-fold increase in the risk of OCSCC. Alcohol use alone contributes only slightly to the risk of OCSCC development, however the combination of cigarette and

alcohol use appears to have a synergistic effect upon the development of OCSCC, increasing the risk 10-15 times (12). Cigarette smoking is the main form of tobacco used in the western world, but the use of smokeless tobacco also carries a significant, albeit lower risk for the development of oral cancer (13). In South-East Asia, South Asia, and India, the use of betel quid (which involves chewing all or various combinations of areca nut, catechu, slaked lime, and tobacco wrapped in a betel leaf) poses a significant risk for the development of oral cancer, contributing greatly to the incidence worldwide (14). Whereas overwhelming evidence has established a role for the human papilloma virus (HPV) serotypes 16 and 18 in the development of oropharyngeal cancer, the association of HPV with oral cancer is much less frequent (15, 16).

The accessibility and visibility of the oral cavity to the patient and clinician makes the diagnosis of OCSCC relatively straight forward. The identification of the clinical features that portend the presence of advanced disease and risk of poor outcome are more challenging and important to distinguish at the time of diagnosis. The AJCC staging system only partially accounts for factors associated with advanced disease (3). On examination, the location and size of the oral cavity mass is important to note. Ulceration is also an indication of aggressive disease, and should be noted. Closer inspection should determine if the mass is fixed to or invading the mandible, tongue mobility should be assessed, and neuropathy of either the second or third division of the trigeminal nerve distribution should be evaluated. The latter finding can be an ominous sign of perineural invasion and spread of disease. The presence of regional nodal disease has a significant impact on disease stage and thus prognosis (3, 6). Any palpable adenopathy should be identified and assessed. The risk of neck disease at presentation is roughly 40-50% (4, 5), and relatively small lesions of the tongue and floor of mouth, with a depth of invasion as low as 2-4 mm, have a 15-20% rate of occult metastasis (17, 18).

The presence of locally advanced disease, particularly invasion of the mandible, pterygoid muscles, tumor involvement of the deep spaces and musculature of the neck, and encasement and invasion of the carotid artery, must be identified during the workup of the patient, as all these factors impact treatment planning and prognosis. The burden of lymph node metastasis must also be accurately assessed. After clinical examination, imaging is crucial in the evaluation of patients with advanced OCSCC. High resolution computed tomography (CT) with intravenous contrast provides excellent detail of the bony, vascular, and soft tissue structures of the head and neck, and is the mainstay for preoperative evaluation. Cortical bony invasion of the mandible is well appreciated with this modality (19), and soft tissue extent of disease, including carotid artery involvement can be evaluated, as well (20). The accuracy of diagnosing pathologically involved lymph nodes based on findings such as lymph node enlargement, loss of the fatty hilar structure, and central necrosis can yield a diagnostic accuracy of roughly 80-90% (21), but the ability to identify extracapsular spread of disease is more limited (21, 22).

Other imaging modalities have been employed to evaluate advanced OCSCC, and can provide complimentary information to that gained from CT scan. Magnetic resonance imaging (MRI) can better delineate the extent of disease involving soft tissue structures, such as the deep musculature of the tongue (23) or perineural invasion (24), and may be better at evaluating the extent of marrow space involvement when there is extensive mandibular invasion (19). The use of ultrasound has been advocated as a practical, less costly, and accurate imaging modality for the evaluation of the cervical lymph nodes for metastases (25-27), but has not gained wide use in the United States for this disease.

During the past decade, fluorodeoxyglucose (^{18}F) positron emission tomography (FDG-PET) alone or combined with CT scan has become widely used for preoperative evaluation and post-treatment assessment of patients with OCSCC. The increased affinity of tumor cells for glucose causes relative accumulation of FDG, and PET scanning can then be used to identify and localize sites of tumor involvement. Though PET scan has been shown to be a powerful tool, and potentially cost-effective for the identification of recurrent disease (28, 29), distant metastasis, and second primary disease (30), the benefit of FDG-PET for the identification of lymph node metastases prior to surgery for OCSCC remains an area of controversy. Recently, Lonneux et al. (31) suggested that pre-treatment FDG-PET could improve the accuracy of TNM staging and alter management in a significant number of patients, however the costs and benefits of this application of FDG-PET is still under debate (32).

In addition to evaluation of the local and regional burden of disease in advanced OCSCC, a metastatic work-up is necessary prior to the formulation of a definitive treatment plan. As mentioned above, if pre-treatment FDG-PET is used, it can be a valuable tool for the identification of distant metastasis (DM), and if applied in patients at high-risk of DM, can be cost-effective (30). If FDG-PET is not employed, chest X-ray or chest CT can be used to rule out the presence of pulmonary metastases. Additional laboratory and imaging tests are used, including a liver function panel and abdominal CT if a high suspicion for hepatic metastases exists. An evaluation of the patients' functional status and a thorough examination of the patient and his or her associated co-morbidities is important to determine if intensive therapy, including surgery, radiation, and systemic cytotoxic chemotherapy, will be tolerated.

SURGICAL TREATMENT

Surgical management of primary site

Treatment for advanced OCSCC requires multi-modality therapy. Surgical resection is the preferred initial treatment modality,

because high-dose radiation to the mandible can result in the development of osteoradionecrosis (33). During the removal of disease in the oral cavity, an attempt is made to achieve a 1-1.5 cm soft tissue margin around gross tumor. When the mandible is involved, marginal mandibulectomy is acceptable if the outer table of cortical bone is not directly invaded by tumor, while segmental resection of the mandible is preferred if there is gross bone invasion (34). Removal of T1 or T2 lesions can often be achieved with little functional deficit and simple closure or reconstruction- examples include partial glossectomy with primary closure, or simple floor of mouth excision with split-thickness skin graft.

When local disease is advanced, a more complex resection and reconstruction is often required. Planning for large resections of the oral cavity can be challenging, and several approaches exist in order to achieve these procedures with the least functional and cosmetic deficits. Two important decisions in approaching the oral cavity involve the necessity to split the lower lip with the incision, and similarly to split the mandible to approach posterior regions of the oral cavity, tongue, and extension to the pharynx (35, 36). The risk of poor healing after mandibulotomy, fistula formation, and the cosmetic result of the lip-split incision must be weighed against the reduced surgical access with a transoral approach or visor flap, and possible functional deficits in chewing or swallowing associated with the lingual-release approach (37). Disease that involves the maxilla or hard palate may necessitate a gingival-buccal incision, or potentially a Weber-Ferguson facial flap for large palato-maxillary resections.

Achieving a surgical margin negative for tumor is of utmost importance. Two large multicenter, randomized-controlled trials have definitively confirmed positive surgical margins as a risk factor for poor outcome (9-11). If disease has spread to the paravertebral muscles, invaded the skull-base, or encased or invaded the carotid artery a negative surgical margin may be difficult or impossible to achieve. In cases where disease is unresectable, other modalities of treatment must be considered. The development and improvements upon the various microvascular free-tissue transfer options now available have greatly improved the cosmetic and functional outcomes for patients with large, complex resections of the oral cavity. Improved reconstruction in the head and neck has greatly enhanced our ability to resect large oral cavity tumors with improved functional outcome, and these are summarized in a separate section below.

Surgical management of the neck

Lymph node metastasis is common in OCSCC, occurring in roughly 45% of patients at presentation (4). Neck dissection, the *en bloc* resection of cervical lymph nodes, has long been advocated for the removal and control of metastatic disease in the cervical region (38, 39). Neck dissection can be both therapeutic and diagnostic. When lymphatic metastases are evident, therapeutic neck dissection often involves complete extirpation of the

cervical lymphatics from all levels of the neck involved with and at risk of having metastases. The original description of the radical neck dissection additionally involved resection of the sternocleidomastoid muscle, internal jugular vein, and accessory nerve (38, 40, 41), but has since been modified to preserve these structures when not directly involved with metastatic disease (42, 43). When extensive disease is present, and removal of the sternocleidomastoid muscle is necessary, either regional or free-tissue transfer is often performed, such as a pectoralis major flap, in order to adequately cover the carotid artery and reduce the risk of carotid artery exposure and rupture. During the last three decades, the decision to perform a modified radical versus a selective neck dissection to treat cervical metastatic disease has become increasingly refined, and the specific indications for these procedures is still under debate. In the current strategy for oral cavity cancer, the literature supports that modified radical neck dissection, where all five levels of lymphatic tissue are removed, is reserved for cases where there is extensive disease, such as the presence of N3 disease, extensive extracapsular spread, or when there is identifiable disease in levels IV or V. In the era of postoperative radiation to the neck after removal of nodal metastasis, selective neck dissection has been used to treat N1 or N2 disease and has yielded outcomes equivalent to those treated with modified radical neck dissection (44-46). For OCSCC, selective neck dissection typically involves removal of levels I, II, and III. Level IV is often removed based on the surgeon's philosophy, and it is still debated when these nodes should be removed or spared in this setting.

When patients present with oral cavity cancer and do not have clinical or radiologic evidence for cervical metastatic disease, a decision must be made for elective resection of the cervical lymph nodes. In these cases, neck dissection can be both therapeutic (i.e., the removal of unidentifiable microscopic disease), and diagnostic (i.e., if microscopic lymph node metastasis is identified, post-operative radiation to the cervical region may be added to the treatment plan). The concept of elective neck dissection was introduced over 50 years ago (39), and a detailed, critical evaluation followed, leading to the development of selective neck dissection for the management of the N0 neck (46, 47). It is generally accepted that lymph node groups with a 15% or greater risk of lymph node metastasis should be electively sampled when clinical disease is not evident. For the oral tongue and floor of mouth, it has been shown that this threshold is breached for tumors with a thickness of 2-4 mm depth of invasion (48), and the lymph node regions at risk for metastasis when disease is localized to the oral cavity are the submental, submandibular, and juglular chain nodes (4, 5, 17). Thus, supraomohyoid neck dissection (levels Ia, Ib, II, and III) is the recommended procedure for elective management of the neck for OCSCC. As described before, elective removal of level IV is under debate. There is evidence that oral cavity cancer can spread to level III or IV at a significant rate without involving upper echelon nodes

(49), but whether this risk of "skip metastases" is high enough to justify risking injury to level IV structures such as the thoracic duct or phrenic nerve remains to be elucidated.

The consideration of bilateral neck dissection for advanced OCSCC deserves some discussion. Advanced tumors of the oral tongue, floor of mouth, lip, and mandible will often encroach or violate the midline of these regions. When this occurs, cervical nodes from both sides of the neck are at risk of developing metastatic disease (50). When disease is not clinically evident, bilateral elective neck dissection is required. For more lateralized disease, the risk of contralateral metastasis without the presence of unilateral lymph node involvement is low, and the presence of unilateral disease after elective dissection will lead to adjuvant radiotherapy to both sides of the neck. Thus, bilateral dissection in these cases is not indicated. Neck dissection to both sides of the neck carries some additional risk, particularly if radical neck dissection is planned. Removal of the jugular veins bilaterally can cause significant increase in intracranial pressure, which has led to the common practice of returning to the operating room at a later date (staged neck dissections) to perform the contralateral lymphadenectomy if it is felt the patient may have to undergo bilateral jugular vein sacrifice (51). Blindness is also a rare, but devastating complication that has been reported (52).

The most recent advancement in the management of the cervical lymph nodes for oral cavity cancer has been the application of sentinel lymph node biopsy (SLNB) for patients with the clinically negative neck. This technique offers a potential compromise between "watchful waiting" and elective neck dissection for patients with primary OCSCC that carries a risk of cervical metastasis. The procedure involves injection of the primary site with technecium-99 sulfur colloid, lymphatic mapping with nuclear scanning, and intra-operative localization with a hand-held gamma probe and subsequent removal of the sentinel lymph nodes for detailed pathologic evaluation. The technique and utilization of SLNB has been well-established for the management of breast carcinoma (53) and melanoma (54), but the application in OCSCC has not been clearly established. A prospective European study reported that the sensitivity of SLNB for the identification of cervical lymph node disease was 93% (55). A more recent prospective multi-institutional trial employed SLNB for 140 patients with T1 or T2 oral cavity cancers, and followed the procedure with completion selective neck dissection (56). The study reported a negative predictive value of 96% and a true-positive rate of 90.2%. Both trials suggested that the accuracy of SLNB was greater for oral tongue cancer than for other sites of the oral cavity, particularly the floor of mouth (55, 56).

The pathologic assessment of the cervical lymph nodes is a crucial component of diagnostic and prognostic workup, and the presence of lymphatic disease weighs heavily on the treatment plan for the patient with OCSCC. The presence of multiple lymph nodes with metastatic disease significantly impacts disease stage (designated Stage IV) and the involvement of greater than 2 lymph nodes has been repeatedly identified as a risk factor that correlates with treatment failure (57, 58) in patients with HNSCC. The presence of extracapsular spread of lymph node disease has been well documented to correlate with poor prognosis (57-59), and was found in two large randomized trials to be an indication for the addition of cisplatin to adjuvant radiation.

SURGICAL RECONSTRUCTION

A variety of reconstruction options exist for oral cavity defects after surgical resection, and methods of reconstruction range from healing from secondary intention or primary closure, to reconstruction with skin grafts, local or regional flaps, to microvascular reconstruction with free-tissue transfer. A detailed discussion of these various options is beyond the scope of this review, but microvascular free-tissue transfer has revolutionized our current management of locally advanced OCSCC and deserves more detailed mention here.

Reconstruction of the tongue has been significantly improved with the use of free tissue transfer. The radial forearm free flap was first used for oral reconstruction in the 1980's (60), and since that time has become one of the primary reconstruction options for large partial glossectomy defects. These reconstructions are associated with improved deglutition and speech for patients after large tongue resections (61-63). The anterolateral thigh flap has more recently been advocated for tongue reconstruction due to its similar versatility and decreased donor site morbidity (64, 65). Total glossectomy defects offer additional challenges. Total glossectomy is a particularly morbid procedure, and the aspiration risk associated with resection of the base of tongue may even necessitate total laryngectomy for functional rather than oncologic indications in some cases. For this reason, chemotherapy and radiation are often offered as primary treatment, with surgery reserved for salvage in these situations. Total glossectomy can be considered without laryngectomy in both primary and salvage cases when the supraglottis is spared (66). Reconstruction of the total glossectomy deficit requires significant tissue bulk for replacement, and this is most often accomplished with the rectus abdominus (67) or lattisimus dorsi free flap (68).

Free microvascular reconstruction of the mandible after segmental resection has become routine for these defects. The fibular free flap is the primary microvascular flap used for mandible reconstruction (64). Several other osteocutaneous flaps have been described for the potential reconstruction of the bony and soft tissue deficits after composite resection of cancer involving the mandible. These include the radial forearm osteocutaneous, scapula osteofasciocutaneous, and iliac crest osteomyocutaneous flaps (64). The use of osseous free-tissue transfer for recon-

struction of the mandible has greatly improved functional and cosmetic outcome in patients with this advanced disease (61, 69).

Large palatal and maxillary defects are repaired with free tissue transfer, as well. Soft tissue free flaps can be used to eliminate oronasal communication after a palatal defect is created (64, 70) . If there is significant loss of the anterior maxilla, a fibular free flap can be fashioned to recreate the projection of the midface and anterior hard palate (64, 70, 71). For small- to moderate-sized defects in the hard palate, obturation is an option for management of the oronasal communication after surgery. The costs and benefits of obturation versus free flap reconstruction have been analyzed (72, 73), but the ultimate decision is a multidisciplinary plan based on the defect, patient factors, and physician preference.

The complex functional and cosmetic deficits that result from composite resection of OCSCC have significant impact on morbidity and quality of life for patients with this disease. Free microvascular tissue reconstruction has greatly increased the ability of the head and neck surgeon to resect advanced local disease with adequate restoration of speech, deglutition, oral competence, and cosmesis.

RADIATION THERAPY

Radiation is not the primary treatment for OCSCC due to the significant morbidity that can result from high dose radiation to the oral cavity, particularly the risk of mandibular osteoradionecrosis (33), as well as the the debilitating mucositis that can ensue. For patients with advanced local disease, or for those with multiple or extensive lymph node involvement, post-operative radiotherapy (PORT) has become the standard of care. No randomized trials have been performed to compare surgery alone to surgery plus PORT for advanced OCSCC, but there is retrospective data that has shown that PORT improves local-regional control and survival in these patients (74-78).

PORT has become widely used for patients with stage III or IV OCSCC. Multivariate analyses have suggested that squamous cell cancer of the oral cavity is linked to a higher risk of local-regional failure as compared to other sites of the head and neck (58, 79, 80). Advanced resectable local disease for which PORT is considered includes those with gross mandibular invasion, extension into the pterygoid musculature, or deep invasion of the tongue. High-risk features, such as perineural invasion, positive surgical margins, or poor differentiation have been associated with reduced local control and certainly justify the recommendation of PORT, even if lymph node disease is not present (58, 79). PORT has also become standard of care for patients with lymph node metastasis. PORT appears to improve local-regional control and survival for patients with two or more metastatic lymph nodes, and extracapsular spread of disease, all of which have been associated with poor outcomes (74-76). These factors

certainly warrant the use of PORT and in the case of extracapsular spread, the addition of concomitant chemotherapy (10). It is unclear if patients with T1-2 local disease with N1 or N2a disease benefit from the addition of PORT to local resection and neck dissection, but retrospective analyses have suggested there may be a benefit for PORT in this subgroup of patients (44, 77).

During the last decade, the toxicity associated with radiation to the oral cavity and neck has been improved with the advent of intensity-modulated radiation therapy (IMRT). IMRT allows the delivery of high-dose radiation to specific sites of the head and neck, with lower dose delivered to adjacent regions that are uninvolved or at lower risk of disease. The radiation dose to important radiosensitive structures, such as the salivary glands, aerodigestive mucosa, spinal cord, and brachial plexus, can be relatively reduced with this method (81, 82). Though few direct comparisons exist, IMRT appears to have equivalent, if not improved efficacy in controlling local-regional disease as compared to conventional 3-dimensional conformal techniques (82-86). IMRT appears to have a decreased rate of toxicity compared to conventional radiotherapy, including improved rates of mucositis, xerostomia, and dysphagia (82, 87)

CHEMOTHERAPY

Since the establishment of combined surgery and radiation for the treatment of advanced OCSCC, several studies have identified factors that appear to correlate with poor outcome despite this treatment (57, 58, 79). Perineural invasion, oral cavity disease site, positive surgical margins, multiple positive lymph nodes, and extracapsular spread of lymphatic disease have been identified as unfavorable factors. During the last decade, studies have evaluated the utility of triple modality therapy, adding concurrent cisplatin to postoperative radiotherapy (88). In 2004, two landmark randomized multi-institutional studies, RTOG 9501 and EORTC 22931, demonstrated the advantages of the addition of platinum-based chemotherapy to postoperative radiation in patients with high-risk, resectable head and neck squamous cell carcinoma (9, 11). Both studies showed improvement in local-regional control and disease-free survival with concurrent cisplatin-PORT, and the EORTC study reported an improvement in overall survival. The RTOG reported increased toxicity and four mortalities from the intensified treatment, whereas the EORTC reported less toxicity and did not have treatment-related deaths (9, 11). Combined review of the two studies clearly defined patients with extracapsular spread of disease and positive surgical margins as a subgroup that derived significant benefit from escalated treatment (10), and these are now definitive indications for the addition of concurrent cisplatin to PORT.

Another advancement in the management of OCSCC was the development and utilization of cetuximab, the humanized monoclonal antibody targeted against epidermal growth factor recep-

tor (EGFR). In 2006, a multi-institutional, randomized phase III trial compared radiotherapy versus radiotherapy plus cetuximab for the treatment of patients with stage III or IV oropharynx, hypopharynx, or larynx squamous cell carcinoma, and showed a significant improvement in overall and disease-free survival for patients treated with cetuximab (89). Though cetuximab has been proven to be an effective agent for concurrent chemoradiation during the primary treatment of disease, a role for post-operative chemoradiation using cetuximab has not been fully established. For some cases of high-risk OCSCC, PORT plus cetuximab may prove to be a useful option with less toxic effects than cisplatin, but further evaluation is necessary.

More recent studies have been conducted to attempt to improve upon the control rates for high-risk HNSCC achieved in RTOG 9501 and EROTC 22931. RTOG 0024 has examined the use of early post-operative paclitaxel followed by a chemoradiation regimen that included both cisplatin and paclitaxel (90). Of the 70 patients enrolled in this phase II study, seven experienced grade 4 non-hematologic toxicity, one experienced grade 4 late toxicity, and one patient died of myocardial ischemia. After adjustment for multiple prognostic variables, this study reported improved local-regional control, disease-free survival, and overall survival as compared to RTOG 9501. A second study, RTOG 0234, examining the tolerability and efficacy of the addition of cetuximab to post-operative chemoradiation, has recently completed. The two arms of this study compared concurrent PORT and docetaxel plus cetuximab versus concurrent PORT and cisplatin plus cetuximab. Preliminary analysis suggests these regimens are tolerated at an acceptable rate, and there appears to be improvement in disease-free survival and perhaps distant control with the docetaxel arm (unpublished data).

As the risk factors for treatment failure become more clear, and the treatments that can be offered to these patients improves, there is a growing need to find ways to intensify treatment while limiting the toxic effects. Although studies such as those described above offer patients with high-risk OCSCC an improved chance at cure, a large portion of patients continue to fail multi-modality treatment.

SALVAGE THERAPY FOR RECURRENT DISEASE

Local and/or regional recurrence can be expected to occur within 5 years in roughly 50-60% of patients with advanced resectable HNSCC treated with combined modality treatment (9, 11). The outcomes of salvage surgery can be favorable in properly selected patients, and the surgeon and patient must weigh the costs and benefits of surgical resection when faced with recurrent disease (91). A recent study reported a median survival of 44.8 months after salvage surgery for patients undergoing resection and free-flap reconstruction for oral cavity recurrence (92). Neck recurrence and a short time to relapse have been associated with a less favorable outcome (92-94).

Surgical salvage offers the best chance at cure for patients with recurrent OCSCC (93, 95). Reirradiation is a modality that has gained increased use in the recurrent setting, and there are several techniques in which this can be employed. If surgery is not an option, either because 1) recurrent disease is unresectable; 2) surgery would lead to unacceptable morbidity; 3) surgery is unsafe due to the patient's medical condition, or 4) patient refusal, then reirradiation with or without cisplatin-based chemotherapy is the best option (96). Reirradiation can be offered as external beam therapy, brachytherapy, and as an adjuvant in the post-operative setting when surgery is feasible (97). There is a high degree of grade III and IV toxicity associated with reirradiation, and when combined with salvage surgery the risks of osteoradionecrosis, tissue necrosis, and the development of orocutaneous and pharyngocutaneous fistulas are increased (96-98). Reirradiation with concurrent cisplatin treatment is increasingly being utilized, and may be a reason for decreased functional outcomes, namely tracheotomy and gastrostomy tube dependence, reported in patients treated with reirradiation during the last decade (96).

When patients present with recurrent disease after initial treatment for oral cavity cancer, it is more important to ask 'what *should* be done?' than to ask 'what *can* be done?' As stated above, surgical salvage is the best chance at cure, but surgical resection of recurrent disease carries a high morbidity rate, especially in the post-radiation setting when advanced disease is present. Patients with early stage recurrence can expect a reasonable chance of being disease-free at two years, however stage 4 recurrence and/or recurrence in the neck carry a median survival of only 9 months (91). Overall, patients with recurrence in the oral cavity appear to have a worse prognosis and a worse quality of life as compared to those with recurrence of laryngeal cancer, although these rates are highly dependent on the stage of recurrent disease (91). When faced with advanced recurrent disease, options other than curative treatment should be considered. Enrollment in a phase I study, palliative treatment including chemotherapy, radiation, or a combination, or perhaps best supportive care in a hospice setting all must be considered when determining the best options to ensure optimal quality of life for the patient suffering with recurrent OCSCC. Treatment of recurrent disease carries a high degree of morbidity, and when the chance at cure is minimal, then every effort must be made to relieve the patient's pain and anxiety. Though hospice care appears to significantly improve these factors for patients with unresectable HNSCC (99), limited data analyzing quality of life in this patient group (100) make it difficult to determine which treatment options are best for patients suffering with advanced recurrent OCSCC. The optimal management strategy for patients with incurable OCSCC is an area which needs improvement and further investigation.

FUTURE ADVANCES IN OCSCC

The treatment of OCSCC continues to evolve as new treatments and strategies are developed and studied. One ongoing challenge is the management of patients with extensive tongue cancer. Outcomes of total glossectomy have improved greatly with the use of microvascular reconstruction (66), but continues to pose significant functional challenges for the patient faced with this procedure. With improved chemotherapeutic agents and technical advances in the delivery of radiotherapy, the role for chemoradiation for advanced oral cavity cancer is being revisited. A recent study reported 6.5% 5-year progression-free survival, and good functional outcome (101) using a chemoradiation strategy for advanced oral cavity cancer. Nine of 49 patients in this study developed oseteoradionecrosis, and these rates must be further compared to those that develop after surgical resection and modern PORT techniques.

Strategies for managing cancer in other sites of the body are becoming increasingly individualized to the molecular profile of a patient's tumor. Treatment options that incorporate a molecular marker into the management of OCSCC have yet to be developed, but genetic alterations in p53 (102, 103) and EGFR (104) have been associated with outcome and response to treatment in HNSCC. Molecular therapy in the treatment of HNSCC has been largely focused on inhibition of EGFR, and several agents are under evaluation (105). The role for these agents as an adjuvant in post-operative concurrent chemoradiotherapy are being established.

CONCLUSION

Treatment for advanced OCSCC requires a multi-disciplinary approach which combines surgery with radiotherapy and cisplatin-based chemoradiotherapy for high-risk cases. Advances in surgical resection and reconstruction, the delivery of radiation, and in chemotherapeutic strategies have improved the management of patients with advanced OCSCC, but the high rate of treatment failure and morbidity of treatment must be improved by future advances in the management of this disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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