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Head and Neck Cancer (CP Rodriguez, Section Editor)

Contemporary Treatment of Locally Advanced Oral Cancer

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Opinion statement

At our institution, locally advanced oral cancer is most commonly treated with surgical resection, immediate reconstruction, and adjuvant radiotherapy with or without concurrent systemic therapy depending on final surgical pathologic analysis. There are patients with markedly advanced local or regional disease who unfortunately will have a low probability of cure. We counsel these patients on induction chemotherapy, emphasizing that this is unlikely to result in a smaller volume of surgical resection. In these patients, a good response to induction chemotherapy is more frequently followed by concurrent chemoradiotherapy. We have not been in the practice of commonly recommending definitive chemoradiotherapy for locally advanced oral cancer when upfront surgery is an option. However, as reviewed below, there is a significant rationale for definitive chemoradiotherapy in patients who are surgical candidates, with the hope of good oncologic outcomes, and potential functional organ preservation. The experts who report their experiences in the studies reviewed below provide a strong argument for considering this approach.

Introduction

Locally advanced oral cavity cancer (LAOC) has variable definitions that include maxillo-mandibular invasion, large tumor size, deep invasion, and extensive subsite involvement [1]. This is a highly morbid and life-

threatening disease. Both disease progression and treatment contribute to functional decline in swallowing, speech, and mastication—a socially isolating situation. Many patients present with significant medical comorbidities that potentiate treatment morbidities and delay recovery. The treatment of such cancers is resource- and time-intensive and can jeopardize the economic well-being of patients and families, even when the patient is health-insured [2, 3]. Treatment courses including surgical resection with reconstruction and adjuvant radiotherapy with or without chemotherapy are standard and can render a patient unable to return to their occupation.

The majority of LAOC cases have squamous cell histology, with approximately 5% of oral cancers showing minor salivary gland, metastatic, or other origins [4]. Most LAOC is attributable to long-term tobacco abuse in both smoking and smokeless forms. While tobacco abuse in the USA continues to decrease, this remains the greatest risk factor [4]. Tobacco consumption remains high in other large countries—in China, consumption is high among younger people, and in India, smokeless chewing tobacco products are widely used. The projected health implications from these practices will plague these countries for decades, while efforts to curb abuse lag far behind the impending health risks. Approximately 10% of LAOC patients have no significant tobacco exposure [5]. Prognosis for these patients is similar to tobacco-using patients. High-risk human papillomavirus (HR-HPV) is not a major risk factor for oral cancers, which are clinically distinct from HPV-associated oropharyngeal cancers in epidemiology and prognosis [6].

Regional metastatic disease to cervical lymph nodes is common in LAOC, and treatment guidelines support neck dissection even in the clinically N0 neck for guiding adjuvant treatment [7]. Additional morbidity of neck dissection is low when performed at the time of the primary site resection, and often, neck exposure is necessary for primary tumor resection and oral cavity reconstruction.

The functional consequences of treatment in LAOC can be both physically and emotionally devastating. Dysarthria, dysphagia, dysgeusia, loss of dentition, trismus, and cosmetic deformity can be lifelong adverse effects of surgery and radiotherapy. Severe osteoradionecrosis can result in long additional treatment courses, many years after cancer therapy is complete. Guiding patient expectations and supporting them in their suffering is a continuous process. Time devoted to pretreatment counseling involves the multidisciplinary team of supporting staff, surgeons, radiation, and medical oncologists, dentists, and speech language pathologists. Finally, tobacco cessation counseling with nicotine replacement and/or other pharmacotherapies is an essential component of the treatment plan—at initial visit, throughout treatment, and longitudinally during tumor surveillance. Continued tobacco smoking is associated with higher recurrence rates and lower survival in head and neck cancer.

Traditional treatment of LAOC has included surgery, radiotherapy, and systemic therapy modalities. Contemporary treatment continues to utilize these approaches. The most common initial approach to LAOC is surgical resection and reconstruction, followed by adjuvant radiotherapy. Oral cavity reconstruction involves versatile options to manage functional consequences when various subsites are sacrificed. However, functional morbidity remains high after surgical treatment of LAOC that may sacrifice the oral tongue and sensory nerves such as the inferior alveolar and lingual nerves. Primary external beam radiotherapy with concurrent chemotherapy—mainly intensity-modulated radiation therapy (IMRT) in the past 15 years—has also demonstrated successful local control in select LAOC patients [8••]. The oncologic success and concomitant risks of osteoradionecrosis with this treatment strategy are reviewed in this chapter. Finally, neoadjuvant systemic chemotherapy has been utilized in LAOC, particularly in markedly advanced cases. In such cases where the need for multimodality therapy is certain, response to neoadjuvant chemotherapy provides important prognostic information. In the postsurgical setting, the indications for adjuvant systemic therapy remain positive margins and nodal extracapsular spread (ECS) [9].

One of the greatest recent advances in cancer therapy has been progressing in systemic immunotherapy, most famously the FDA approval of checkpoint inhibitors such as the anti-PD-L1 and anti-PD-1 inhibitors, pembrolizumab and nivolumab, for patients with recurrent or metastatic head and neck cancer who have tumor progression after platinum-based chemotherapy. Ongoing window-of-opportunity clinical trials are also exploring various systemic therapy combinations in the neoadjuvant setting.

This chapter will review advances in the treatment of LAOC, with a brief overview of surgical resection and reconstructive approaches and greater emphasis on organ preservation strategies. The rationale for and outcomes of definitive chemoradiotherapy protocols will be explored, as well as the role of immunotherapy in the treatment of recurrent disease.

Surgical management

A technical description of oral cavity reconstruction for LAOC is beyond the scope of this chapter. Select principles and subsite considerations for reconstruction will be reviewed here. The subsites of the oral cavity include the buccal mucosa, retromolar trigone, alveolar ridge, oral tongue, floor of mouth, hard palate, and lips. While surgery followed by adjuvant radiotherapy with or without chemotherapy remains the most common approach to treating LAOC, it is sobering to acknowledge the morbid suffering that patients endure as a result of tumor resection. A sub-total glossectomy for locally advanced oral tongue cancer, for example, has devastating effects on speech, taste, and swallow function. Resection of large buccal and retromolar trigone tumors may result in severe trismus. Floor of mouth tumor resections carry the risk of tongue contracture and tethering, again affecting speech and swallowing. Composite mandible or maxillary resections can alter dentition, occlusion, lip sensation, and cosmesis.

LAOC of the oral tongue or floor of mouth often involves both of these subsites, and reconstructive considerations include: [1] maintenance of tongue mobility ideally to achieve premaxillary contact for optimal speech, [2] creation of adequate bulk of the neo-tongue for swallowing and speech, and [3] restoration of the floor of mouth sulcus that may become blunted with reconstruction. A blunted floor of mouth may preclude usage of a patient's dentures.

Thorough surgical planning must anticipate the size and three-dimensional contour of the resection bed, the functional consequences of disrupted subsites, and patient-specific priorities. For example, an 80-year-old edentulous gentleman who does not wear dentures, with a retromolar trigone cancer and local bony invasion, may feel little value for osseous mandibular reconstruction after segmental mandibulectomy. In his case, soft tissue reconstruction of the surgical defect may provide intraoral lining, mitigate any external contour deformity, and reduce the risk for trismus. A similar tumor in a 50-year-old fully dentate patient requires the same functional considerations, in addition to the restoration of mandibular continuity that can withstand the load of mastication. The fibula osteocutaneous free tissue transfer is the most commonly employed flap for maxillo-mandibular reconstruction. Commercially available three-dimensional virtual planning and custom design of reconstruction plates are commonly utilized for precise reconstruction. The cost of these services can exceed $10,000 per case, and many surgeons cite the ability to achieve precise reconstructive results without such technologies. Conversely, some surgeons contend that customized preoperative planning reduces operative time and cost.

One of the most important principles to acknowledge on the surgical ablative side is the expectation that negative resection margins are achieved. Surgical debulking, or partial tumor resection, do not have a known role in LAOC, given the aggressiveness of this disease. The breadth of reconstructive options for LAOC is immense, with subsite involvement, patient values, and medical comorbidity as major considerations in the selection process. An additional discipline in cancer reconstruction is respect for the oncologic treatment timeline—i.e., avoiding delays in adjuvant therapy related to surgical healing.

The following section discusses experience with definitive chemoradiotherapy in the treatment of LAOC. While this approach is less commonly used, experienced cancer centers have been able to achieve good oncologic outcomes. The functional and toxicity profiles of this strategy are also reviewed.

Primary chemoradiotherapy or radiotherapy

While multimodality therapy for LAOC is most frequently initiated with primary surgery, primary chemoradiotherapy (CRT) is a rational approach that has also shown successful outcomes. Patients with stages III and IV oral cancer, including those with advanced primary tumors and/or advanced nodal disease have been treated with definitive chemoradiotherapy. No randomized controlled trial has been specifically designed to compare primary surgery with adjuvant therapy to definitive chemoradiotherapy in LAOC. Numerous retrospective studies have evaluated this comparison, with several important studies summarized here.

Some retrospective studies have demonstrated inferior overall survival and locoregional control in patients receiving definitive chemoradiotherapy or radiotherapy (RT) alone compared to those treated surgically [8••, 10–12]. Previous studies have reported a 5-year locoregional control (LRC) of 49–79%, disease-specific survival (DSS) 30–39%, disease-free survival (DFS) 22–76%, and overall survival (OS) 22–63% for patients undergoing definitive chemoradiotherapy compared to LRC 77–86%, DSS 45–64%, DFS 45–68%, and OS 45–54% for patients undergoing surgery with adjuvant (chemo) radiotherapy [8••, 10, 11, 13•, 14]. A hospital-based study of the National Cancer Database suggested treatment with definitive chemoradiotherapy was associated with more advanced T and N stages, and advanced age—when compared to patients undergoing primary surgery [10]. Likewise, in a single-institution retrospective study comparing definitive chemoradiotherapy (100 patients) to primary surgery with adjuvant therapy (109 patients) for LAOC, improved locoregional control was observed in the surgical group on multivariate analysis (HR 2.88, 95% CI 1.35–6.16) adjusting for covariates including tobacco and alcohol usage, but not tumor diameter and N stage [10]. Indeed, patients receiving definitive chemoradiotherapy had more advanced clinical T and N staging. While DFS and DSS were also superior in the surgical group on log rank testing of Kaplan-Meier survival curves, this did not remain significant after adjusting for confounders such as tumor diameter and age. Another single-institution comparison of definitive chemoradiotherapy (50 patients) to primary surgery (54 patients) showed improved LRC and DSS in the surgical group after adjusting for higher T stage, N stage, comorbidity, and tumor subsite [10]. A

clear, consistent challenge in retrospective comparison of definitive chemoradiotherapy and primary surgery with adjuvant therapy has been confounding of survival outcomes results with imbalanced local and regional pretreatment staging, and in some studies, the older age for the nonsurgical treatment group. Lower locoregional control and overall survival in the definitive chemoradiotherapy groups may be explained in part by more advanced pretreatment stage.

One of the largest retrospective series to study oncologic and toxicity outcomes in patients with LAOC receiving definitive chemoradiotherapy reported considerable success. A total of 140 patients with locally advanced stages III/IV oral cancers were treated over a 20-year period. In this study, 106 of 140 (75%) patients had clinical T3 and T4 disease, 85 of 140 (61%) had clinical N2b or greater nodal disease, and 128 of 140 (91%) had stage IV disease [8••]. Chemotherapy regimens primarily included 5-fluorouracil (5-FU) and hydroxyurea, while a smaller proportion of patients also received taxane, platinum agents, or cetuximab, an epidermal growth factor receptor (EGFR) inhibitor. Over the course of the studied period, the radiotherapy platform evolved to intensity-modulated radiotherapy (IMRT), with typical dosing of 70–75 Gy to gross disease, and lower dosing to surrounding at-risk volumes. With a median follow-up of 5.7 years, the 5-year survival outcomes were overall survival (OS) 63.2%, progression-free survival (PFS) 58.7%, locoregional control (LRC) 78.6%, and distant control (DC) 87.2%, considerably improved over prior studies. While univariate regression analysis reported T4 (versus lower T stage) and floor of mouth primary site (versus all others) to be associated with worse PFS and OS respectively, no variables remained significant predictors of any survival outcome in a multivariate analysis.

The acute and long-term morbidity of definitive chemoradiotherapy was also studied [8••]. There were nine deaths in this study attributable to treatment toxicity. Five of these patients died of sepsis. The authors used the validated Swallowing Performance Status Scale (SPSS) to evaluate posttreatment swallow function [12]. This data was available in 89 of 140 patients, and 10% of these were gastrostomy tube (G-tube). Previous studies have reported rates of enteral support ranging from of 3–27% [14, 15]. It was unclear at what time point the SPSS was assessed in this study, and whether additional patients progressed to G-tube dependence or whether some G-tube-dependent patients eventually returned to full oral intake. Information was not available on the quality and social aspects of oral intake after treatment or speech performance. In this study, 82 patients had information on osteoradionecrosis (ORN) available and 20.7% developed ORN that required surgery. As is difficult in retrospective study, the proportion of patients with known, symptomatic ORN managed non-surgically could not be captured. Oral cavity subsite analysis was limited by small sample size, but the subsite associated with the highest ORN rate was the floor of mouth (8 of 17; 47.1%) on univariate analysis. Other retrospective series have reported ORN rates after definitive chemoradiotherapy of 4–18% [11, 13•, 15–17], compared with rates as low as 1.3% in patients undergoing surgery with adjuvant radiotherapy [18].

Despite the significant morbidity of ORN recognized in the prior study, the reasonable overall survival and locoregional control achieved with definitive chemoradiotherapy for LAOC were compelling. As the authors noted, the discrepancy between their oncologic outcomes and poorer outcomes in prior retrospective studies may be attributable to patient selection bias surrounding

the choice for primary chemoradiotherapy. It is possible that older patients and those with more advanced locoregional disease pursued definitive chemoradiotherapy over surgery [10], whereas treatment algorithms in the aforementioned study may have had more emphasis on selecting healthier patients with LAOC for definitive chemoradiotherapy [8••].

Given the successes of organ preservation protocols with concurrent chemoradiotherapy for the treatment of advanced laryngeal and pharyngeal cancers [19, 20], a similar interest in LAOC is logical. Limited data from the randomized treatment SHN01 trial was reported first in 2005 with a 10-year follow-up in 2015 [21, 22]. This trial randomized patients with locoregionally advanced head and neck cancers of the larynx, hypopharynx, oropharynx, oral cavity, and maxillary sinus to surgery with adjuvant therapy or definitive chemoradiotherapy. Only 32 of 119 patients had oral cavity cancer, and therefore, subsite analysis was limited. Of the oral cavity cancer patients, the 5-year reported DSS was 68% among 19 patients in the surgical group and 12% among 13 patients in the definitive chemoradiotherapy group. Investigators reported trial closure before complete accrual, as many patients elected for nonsurgical treatment without study participation.

Definitive chemoradiotherapy may have an underutilized role in the treatment of LAOC, but clinically balanced comparisons of primary surgery to definitive chemoradiotherapy are difficult to construct. Limited recent data demonstrates the success of definitive chemoradiotherapy in LAOC patients that can be achieved with careful patient selection. Prior investigations show that the most significant confounders—tumor inoperability, advanced comorbidities, or advanced disease—likely obscure considerable oncologic success with organ preservation protocols [8••].

Contemporary advances

Immunotherapy

Locally advanced oral cancer continues to have high morbidity and mortality rates despite advances in surgical and radiotherapy precision. Recent progress in tumor immunotherapy has expanded options for LAOC patients and catalyzed the design of novel clinical trials and research directions. In principle, the relatively high mutational burden of head and neck squamous cell carcinoma and tumor-specific antigenicity should promote relatively robust responses to immunotherapies such as Anti-PD-1 or Anti-PD-L1 medications [23].

The Anti-PD-1 receptor antibody pembrolizumab (Keytruda) was approved in 2016 by the Food and Drug Administration (FDA) for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma that had progressed after treatment with a platinum-based systemic agent. The results of a subsequent randomized open-label phase 3 trial (KEYNOTE-040) comparing monotherapy pembrolizumab to standard methotrexate, docetaxel, or cetuximab were recently reported. Again, for patients with recurrent or metastatic head and neck squamous cell carcinoma having previously received platinum-based treatment—a small but statistically significant increase in overall survival was observed in the pembrolizumab group compared to standard therapy (median 8.4 months versus 6.9 months, respectively; HR 0.8, 95% CI 0.65–0.98) [24••]. The response to pembrolizumab was more durable, and the adverse effect profile was less severe. Tumors were also assayed for PD-

L1 expression, which showed improved overall survival in expressors treated with pembrolizumab relative to standard therapy. Durable responses continue to be reported from the original phase 1b KEYNOTE-012 trial for a small proportion of patients receiving pembrolizumab for over 2 years [25]. A more recent KEYNOTE-048 trial studied pembrolizumab with or without platinum-based therapy as first-line treatment for recurrent or metastatic head and neck squamous cell carcinoma and demonstrated significant improvement in overall survival and response duration in patients treated with pembrolizumab compared to the standard treatment, as well as a favorable side effect profile [26].

The Anti-PD-1 antibody nivolumab (Opdivo) was also FDA approved in 2016 for the same advanced head and neck cancer population. Recently, a case report showed a robust, near complete tumor response to combination nivolumab with the anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody, ipilimumab (Yervoy) in one patient with an oral cancer recurrence. This patient had oral tongue cancer and underwent primary surgery and adjuvant chemoradiotherapy. After tumor recurrence in the neck, he had persistent disease while receiving combination of 5-FU, cisplatin, and cetuximab, and the tumor was found to express PD-L1 [27].

The authors of this current article have also cared for one patient who had suffered an aggressive recurrence of oral cavity squamous cell carcinoma after composite floor of mouth and mandibular resection, fibular free tissue transfer for reconstruction, and adjuvant radiotherapy. She had marked tumor progression despite standard systemic therapy and experienced a complete response to nivolumab that has remained durable for over 3 years. Reports of such enthusiastic responses are rare but support the hope that a new era of cancer treatment is rapidly evolving.

Window-of-opportunity studies

Neoadjuvant therapy may be considered in oral cancer patients wherein very advanced local or regional disease is present and any curative attempt clearly requires multimodality therapy. While the response to systemic therapy rarely facilitates a smaller resection volume, and previous studies on induction chemotherapy have not demonstrated improvement in clinical outcomes, it may provide valuable prognostic data as to a patient's probability of responding to multimodality therapy [28–30]. This can be of immense importance for patient counseling while anticipating the probability of successful curative treatment. Window-of-opportunity trials aim to study the response to drugs during the interval between diagnosis and definitive therapy. Several such studies involve oral cancer patients. The SNOW-001 (NCT03575598) phase 1 trial opened in August 2018 and combines nivolumab with a multi-kinase inhibitor sitravatinib. Eligible patients must have oral cavity squamous cell carcinoma that is considered resectable. Again PD-L1 expression and immune cell population density will be measured, in addition to secondary clinical outcomes including tumor treatment effect, rate of postoperative complications, and rate of disease progression. In 2017, a phase 2 study of stages II–IV oral cavity squamous cell carcinoma patients treated prior to surgery with the Mek1/2 inhibitor trametinib reported decreased p-ERK1/2 and CD44 expressions in some study participants. This indicated reduced Ras/MEK/ERK pathway

activation—an important pathway in oncogenesis [31]. A reduction in tumor metabolic activity as measured by PET imaging SUV_{max} was also observed. In this study, 9 of 17 (53%) patients had downstaging of their disease, when comparing presurgical clinical staging to postsurgical pathologic staging. Window-of-opportunity trials are providing assessment of oral cancer response to an increasing number of systemic therapies, with the benefit of surgical pathology for tumor response data that may inform subsequent treatment strategies.

Compliance with Ethical Standards

Conflict of Interest
David Kim and Ryan Li declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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