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REVIEW

Primary Management of Operable Locally Advanced Oral Cavity Squamous Cell Carcinoma: Current Concepts and Strategies

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ABSTRACT

Introduction: Locally advanced oral cavity carcinoma (LAOCSCC) is primarily treated with surgery followed by radiotherapy with or without chemotherapy.
Methods: A review of literature using PubMED was performed for studies reporting the management of LAOCSCC. Based on the reviewed literature and opinions of experts in the field, recommendations were made.
Results: Studies have shown that outcomes following resection of T4a and infranotch (inferior to mandibular notch) T4b are comparable. We discuss the concept of compartmental resection of LAOCSCC and issues concerning the management of the neck. Further, patients who refuse or are unable to undergo surgery can be treated with chemoradiotherapy with uncertain outcomes. The role of neoadjuvant

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chemotherapy has shown promise for organ (mandibular) preservation in a select subset of patients.
Conclusion: The management strategy for LAOCSCC should be determined in a multidisciplinary setting with emphasis on tumor control, functional preservation, and quality of life of the patient.

Keywords: Oral cavity squamous cell carcinoma; TNM; Margins; Neoadjuvant chemotherapy, surgery

Key Summary Points

Surgery with clear margins followed by radiation therapy, with or without chemotherapy, is the mainstay of treatment in locally advanced oral cavity squamous cell carcinoma (LAOCSCC).

3D digital modeling has potential to be a valuable adjunct to intraoperative margin assessment protocols as software for these solutions is developed.

Compartmental resection involves removal of the entire anatomical compartment including the musculature and neurovascular components along with the fascial components. Studies have shown that selected patients with T4b OCSCC with masticator space involvement can be treated with a curative intent with reasonable functional outcomes.

Virtual surgical planning (VSP) is being increasingly used in the reconstruction of complex head and neck defects. VSP encompasses computer aided design/computer assisted manufacturing (CAD/CAM) and creation of defect specific 3-dimensionally (3D) printed models.

The role of neoadjuvant immunotherapy is an emerging topic that remains incompletely defined for oral cavity squamous cell carcinoma at this time.

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INTRODUCTION

Despite increased oral screening programs and advances in diagnostic modalities in detecting oral cancers at an early stage, a disproportionately high number of patients are still diagnosed in advanced stages [1–3]. Nearly 55% of patients with oral cavity squamous cell carcinoma (OCSCC) present with locally advanced stage disease. Locally advanced oral cavity squamous cell carcinoma (LAOCSCC) portends a poor prognosis with a 5-year survival of about 40–50% [4]. Multimodality treatment is warranted in LAOCSCC with surgery being the mainstay of the treatment followed by adjuvant radiation therapy (RT) with or without chemotherapy [5, 6]. Surgery entails wide excision with adequate margins, neck dissection, and appropriate reconstruction [5]. The concept of compartmental surgery has been described in operable LAOCSCC with reasonable oncologic and functional outcomes [7]. However, a significant number of patients have comorbidities which may preclude many patients from getting optimally treated, especially with surgery [8]. This may have a negative impact on survival outcomes in these patients [8]. Although the role of neoadjuvant chemotherapy or immunotherapy for operable LAOCSCC is limited, its role for organ (mandibular) preservation in a select group of patients has shown some promise [9]. This review will discuss the contemporary management paradigms for primary operable and borderline-operable LAOCSCC which are treated with a curative intent. As the review is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, no ethical approval was necessary.

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DEFINING LOCALLY ADVANCED ORAL CAVITY SQUAMOUS CELL CARCINOMA (LAOCSCC)

The 8th edition of American Joint Committee on Cancer (AJCC) stratifies LAOCSCC into moderately advanced local disease (T4a) and very advanced local disease (T4b) [10]. Involvement of the floor of mouth, inferior alveolar nerve, cortical bone or the skin along with a depth of invasion (DOI) of more than 10 mm and/or tumors more than 4 cm in size render the disease T4a whereas involvement of the masticator space, pterygoid musculature, involvement of the skull base, carotid vessels or the prevertebral fascia upstages the disease to T4b. Staging helps in selecting the appropriate management strategy and triaging patients into surgical or non-surgical management [10]. The terms operable and resectable are often used interchangeably; however, there is a key difference between the two. While resectability is governed by the anatomical extent of the cancer and its proximity to important structures, operability is influenced by the ability to achieve oncologically safe outcomes including negative margins as well as a reasonable morbidity and survival after surgery. Thus, involvement of structures like the prevertebral fascia, skull-base or encasement of the internal carotid artery are all signs of unresectable tumors. However, in borderline cases, assessment of resectability should be considered on a case-by-case basis (Table 1).

SURGICAL PRINCIPLES AND PATIENT SELECTION

Surgery with clear margins, neck dissection, appropriate reconstruction, and acceptable morbidity is the mainstay of the treatment for LAOCSCC followed by RT or chemoradiotherapy (CRT) [5]. Oncologic clearance is challenging in advanced disease given the alteration of the complex 3-dimensional (3D) anatomy in locally advanced tumors. Finally, as a result of the high incidence of regional neck metastasis in OCSCC, treatment algorithms include neck dissection in clinico-radiologically negative necks (N0) as well [5]. This approach is further supported by the frequent need to access the neck to provide additional exposure for larger tumors as well as to facilitate reconstruction of the post ablation defect [6].

Cross-sectional imaging with contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) is critical for determining the extent of the locoregional disease and to determine operability [11]. CECT is the most used modality for the majority of patients with LAOCSCC. CECT has a high sensitivity and specificity for bone erosion and for carotid artery and skull-base involvement [12, 13]. Neto et al. reported the findings of their meta-analysis comparing MRI and CT scan in detecting mandibular invasion in oral cancer. The authors did not observe a distinct advantage of either modality in detecting mandibular invasion [14]. The summary receiver operating characteristic (sROC) was 82.3% and 82.5% for MRI and CT scans, respectively [14]. Recent developments have increased the use of a higher field MRI such as 3 T MRI in clinical settings. Theoretically, 3 T MRI produces higher resolution images [15]. Diagnostic accuracy of various protocols including the conventional two-dimensional fast spin echo (2D FSE) sequence, 3D volumetric interpolated breath-hold examination (3D VIBE), and modified fast 3D T1-weighted gradient-echo sequence were compared to 64-row multidetector CT (MDCT) to detect mandibular erosion in a study by Suzuki et al. [16]. MDCT showed a higher specificity (89%) than any of the three sequences used for the 3 T MRI for mandibular invasion. Interestingly, the specificity of the 2D FSE sequence was significantly lower than that of MDCT (56% vs. 89%, respectively; $p < 0.017$) [16]. Soft tissue delineation, however, is better demonstrated with MRI along with bone marrow involvement in the absence of cortical bone erosion [17]. Another crucial aspect of LAOCSCC is major nerve invasion or perineural invasion. Around 5–10% of patients present with perineural invasion. Sensitivity of MRI in detecting perineural invasion has been reported in several studies up to 95% [18–20]. MRI plays a crucial role in determining prevertebral fascia involvement as CT scan has a lower specificity when compared to an MRI (88.2% vs. 99.2%, respectively) [21, 22]. Preservation of the retropharyngeal fat plane is key to determining the involvement of prevertebral fascia as signs like concavity of the ipsilateral muscle or muscle hyperintensity on T2 can mimic peritumoral edema without actual muscle involvement [23]. Overall, CECT is the preferred modality of imaging in OCSCC when evaluating for bony erosion and contrast-enhanced MRI may be preferred when soft tissue delineation is more important such as in cancers of the tongue or the floor of mouth. However, the choice of imaging modality largely depends on surgeon preference, availability of expertise, and cost to the healthcare system.

18-Fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG-PET/CT) is the most used nuclear imaging modality in the workup of head and neck cancers. Cross-sectional imaging provides the extent of the tumor which is critical in surgical planning and assessing operability. 18-FDG PET/CT, however, lacks applicability in this aspect. Traditionally, this stems from the fact

Table 1 Anatomical structures amenable to surgical management in T4b oral cavity squamous cell carcinoma (OCSCC)

Surgery as a preferred modality	Avoid surgery
Masseter muscle, lower part of medial pterygoid muscle	Pterygoid plates
Ascending ramus of the mandible	Prevertebral fascia
Edema extending to the zygoma	Internal carotid artery/common carotid artery
	Lateral pterygoid muscle, tendon of the temporalis muscle
	Skull-base bones

that 18-FDG PET/CT has a lower resolution than CT or MRI in delineating the anatomic detail required for surgical planning [24]. In recent years, 18-FDG PET/CT has been performed with intravenous contrast and improved quality of CT scans. This may be beneficial in cases where delineation of the tumor is difficult with the streak artifacts in CT scans or metal/motion artifacts with MRI [25]. Studies have shown that whole body 18-FDG PET/CT in OCSCC has the most utility in detecting cervical lymph node metastasis, second primary malignancies, distant metastasis, and early postoperative recurrence [26–30].

Surgical Margins

Clear margins have a positive impact on survival outcomes in OCSCC with an absolute risk reduction of 21% (95% CI 12–30%, $p < 0.00001$) in local recurrence rates as reported by a meta-analysis published in 2015 [31]. Several studies have also stressed the importance of the status of resection margins, either positive or negative, and the impact they have on survival [31, 32]. In fact, a National Cancer Database (NCDB) database study showed a higher rate of positive margins in cT4b OCSCC than in cT4a OCSCC (30.4% vs. 21.3%, $p = 0.009$) [33]. However, the best cutoff distance from invasive cancer for a close or clear margin in the pathological examination is somewhat nebulous. Clear margin is defined by the National Comprehensive Cancer Network (NCCN) as resection margin being more than 5 mm from the invasive cancer [5]. Historically the histologic 5-mm cutoff has been used to define close and clear margins. However, recent studies have questioned the evidence for this cutoff. Studies have shown that margins of 1–5 mm did not adversely affect the survival outcomes in OCSCC [34–38]. Most cases included in those series are of early-stage disease though. Jang et al. reported for advanced stage there was a negative impact on survival if the margins were less than 5 mm [39]. Köhler et al. reviewed a series of 772 patients submitted to oral cancer resection with free or close margins. In the cases of tumors with worst pattern of invasion classified as 1–3, the best cutoff of margins was 1.7 mm; on the contrary, for the cases with worst pattern of invasion (WPOI) 4 or 5, the test cutoff was of 7.0 mm [40]. Furthermore, to achieve 5-mm margins in pathological examination, it is necessary to have up to 10-mm margins delineated by visual inspection and palpation during the surgical performance because surgical margins of the excised specimen can shrink up to 47% from before excision to the pathologic examination [41–43].

Tools for Surgical Margin Assessment

Specimen driven intraoperative frozen section margin determination is typically the favored method of real-time margin assessment [10]. Various imaging techniques are under investigation to improve the status of the surgical margins. Many in vivo as well as ex vivo intraoperative assessments have been reported. Mucosal staining methods, optical coherence tomography, and narrow band imaging can be used for mucosal resection margin control. For deep margin control, in vivo techniques include ultrasound-guided resections. Promising ex vivo techniques are ultrasound, MRI, PET, and targeted fluorescence imaging [44]. In a pilot study of 40 patients with OSCC, ultrasound-guided resections improved margin status (55% vs. 16% adequate margins) and reduced the frequency of adjuvant treatment (30% vs. 20%) when compared to a historical cohort [45]. However, T4 tumors were excluded from the study. Recently, the use of 3D anatomical specimen for intraoperative margin assessment has been studied. Saturno et al. published the results of their "proof-of-concept study" wherein 3D models of gross tumor specimen were generated and inked virtually using the paintbrush tool within Microsoft Paint 3D [46]. The software was able to recreate the color contrast and geometric complexity of the specimen surfaces, with distinct anatomical landmarks with minimal distortion. Authors noted that their scanning workflow was easily integrated into the routine frozen section protocol and the margin results were reported within an average of 34 min [46]. This optical scanning tool is distinct from the 3D models created from sections of histological slides or from 2D sectional imaging preoperatively [47, 48]. Further, the diagnostic accuracy of frozen section and MRI for assessing intraoperative surgical margins has been described. Specifically, the authors utilized a 3D-printed, patient-specific tongue model to examine the surgical specimen and showed that integrating frozen section with ex vivo MRI provides a more accurate assessment of intraoperative surgical margins. Although these were preliminary results they do warrant further studies with higher sample size [49]. Although still evolving, 3D digital modeling has potential to be a valuable adjunct to intraoperative margin assessment protocols as software and these solutions are developed.

Masticator Space and Operability

Traditionally, the standard of care for the T4b subset of patients has been chemotherapy and/or RT with a palliative intent in most cases or clinical trial enrollment [5]. This is especially true for tumors invading the skull-base, prevertebral fascia, and tumors encasing the internal carotid artery. Masticator space involvement also upstages the disease to T4b and is conventionally considered inoperable. Tumors of the buccal mucosa are the most common subsite of the oral cavity that involves the masticator space. Locoregional failure is more common than distant failure in these tumors [50]. Involvement of the masticator space makes the surgery challenging because of the complex 3D anatomy of this region and the ability to achieve clear margins [51].

Liao et al. proposed the concept of supranotch and infranotch T4b OCSCC based on a horizontal plane passing through the mandibular notch based on a CT or MRI (Fig. 1). Forty-five consecutive patients treated with primary surgery were studied. Authors reported a significantly higher 5-year locoregional control (LCR) (74% vs. 42.9%, $p = 0.0254$) and OS (55.3% vs. 14.3%) in patients who had infranotch disease than supranotch disease [52]. The same group reported the results of 181 pT4 patients who underwent radical resections. Only infranotch T4b tumors as described above were included in the T4b group. The authors concluded that infranotch pT4b tumors had comparable outcomes when compared to pT4a tumors [53]. Mair et al. proposed a treatment protocol based on their experience in treating T4a/T4b patients. Infranotch disease which involved the masseter, the ascending ramus of the mandible, and the lower portion of the medial pterygoid fared better with upfront surgery and followed by CRT or RT based on the final histopathology report. Whereas supranotch disease which involved the lateral pterygoid muscle, the tendon of the temporalis muscle and the upper third of the pterygoid plates as well as peritumoral edema above the zygoma could be treated with neoadjuvant chemotherapy, and if response was good one could consider surgery and CRT but if no response was obtained then one could consider CRT/RT/palliative chemotherapy [53]. The authors reported similar results in the 3-year LCR of 71.1% vs. 61.8%, $p = 0.107$ and OS of 49.6% vs. 41.1%, $p = 0.518$ between T4a and infranotch T4b patients, respectively [54]. Another study showed that lateral pterygoid muscle involvement has been seen as an independent predictor of poor outcome in T4b tumors [55]. Rai et al. proposed to reevaluate the current AJCC staging system as survival differed significantly among patients with limited masticator space involvement versus tumors which had internal carotid artery invasion and/or invasion of the skull-base structures [51]. A propensity matching study from Taiwan, which included 702 patients, demonstrated that once propensity score matching is achieved for positive margins between pT4a and pT4b tumors, there is no survival difference between surgically resected T4a and T4b tumors. Thus, the authors recommended that when adequate surgical margins are achievable, T4b tumors must be considered operable [56]. A recent meta-analysis reported comparable surgical outcomes in infranotch T4b disease and T4a disease [57]. Baddour et al., however, reported the survival outcomes in 25 patients with T4b OCSCC with pathologic masticator space involvement who underwent primary surgery

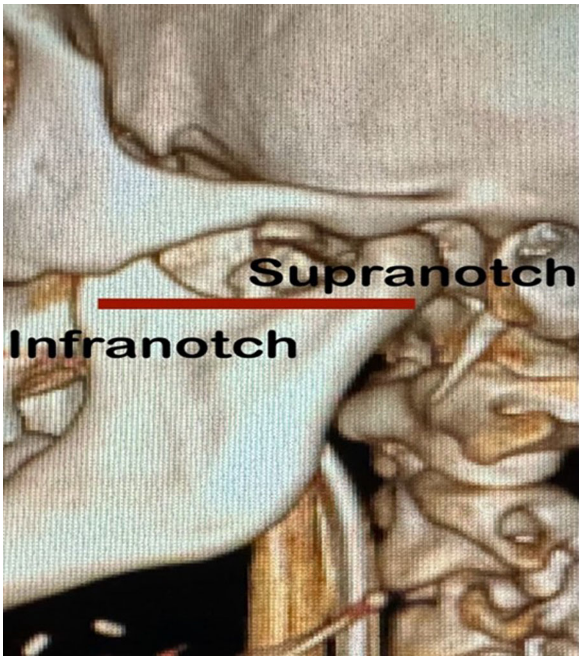

Fig. 1 Anatomical categorization of supranotch and infranotch T4b cancers

followed by adjuvant therapy. The 2-year OS and disease-free survival (DFS) were 44% and 63.2%, respectively [58]. There was no difference in survival outcomes between supranotch and infranotch disease in this patient cohort, which the authors attributed to the smaller sample size in both groups [58].

Concept of Compartmental Resection

Compartmental resection in OCSCC was first introduced by Calabrese and colleagues in 2009 for oral tongue cancers. It has been reported that compartmental surgery achieves better oncologic outcomes when compared to traditional surgery wide margins (1–2 cm) [59, 60]. Compartmental resection involves removal of the entire anatomical compartment including the musculature and neurovascular components along with the fascial components. Calabrese and colleagues reported decreased risk of local (hazard ratio (HR) 0.31, 95% CI 0.13–0.72; $P = 0.006$) and locoregional recurrence (HR 0.36, 95% CI 0.17–0.80; $P = 0.011$) when compartment surgery was compared to standard transoral tongue resection, at 5 years. There was no difference in distant failure at 5 years (HR 1.90, 95% CI 0.55–6.51; $P = 0.31$) between the two approaches [60]. Missale et al. compared patients undergoing wide local excision and compartmental surgery and reported comparable oncologic outcomes when propensity matched. The 5-year locoregional recurrence-free survival between compartmental surgery and wide local excision was 75% vs. 64%, respectively and DFS was 66% vs. 55%, respectively in this study [61].

Trivedi et al. described the compartmental resection in T4b buccal mucosa cancers, involving the masticator space. The contents of the masticator space were removed en bloc regardless of their involvement to include the mandible, masseter muscle, temporalis muscle, and medial and lateral pterygoids from origin to insertions. Partial maxilla or upper alveolus was included in the resection, if indicated. Resection involved removal of the soft tissue up to the infratemporal fossa (ITF), including the pterygoid plates [62]. Mohiyuddin et al. reported the results of 52 patients with T4b OCSCC extending to the ITF who had an OS of 60% at 30 months follow-up [63]. Similar to the findings reported in other studies, disease involving the posterior half of the mandible and the pterygoid plates had poor survival outcomes. Local control rates reported in these studies ranged between 53% and 60% [61–64].

In the study by Trivedi et al., 71% of patients resumed oral soft diet and had reasonable communications skills [62]. Lip continence and cosmesis were reported as satisfactory in most patients as well [65]. Reasonable functional outcomes were also reported by Grammatica et al. and Carta et al. in patients who underwent compartmental surgery for oral tongue cancer and free flap reconstruction [66, 67]. In a cohort of 48 patients reported by Grammatica et al., more than 50% patients reported the perception of their swallowing as good/satisfactory using both European Organization for Treatment and Research (EORTC) and University of Washington Quality of Life (UWQOL) questionnaires. However, more than 50% patients in the same study considered their speech to be less favorable on UWQOL questionnaire [66].

Ren et al. described the concept of unit-based buccal surgery for tumors originating in the buccal mucosa. The buccal mucosa was divided into pregena and postgena and by the line of occlusion. Similar to compartmental resection, surgery involved removal of the entire subunit in which the tumor is contained rather than the conventional 1–2 cm margin. The authors emphasized that the principles of unit-based surgery can be applied to all stages of the disease and especially advanced stage OCSCC [68].

Whilst these studies have shown that selected patients with T4b OCSCC with masticator space involvement can be treated with a curative intent with reasonable functional outcomes, studies with larger sample size are needed for compartmental resection to become a standardized surgical technique in LAOCSCC.

Virtual Surgical Planning in Reconstruction

Although detailed discussion of principles of head and neck reconstruction is beyond the scope of this review, we will discuss the principles and rationale of virtual surgical planning (VSP) which has been increasingly incorporated in reconstruction protocols for complex head and neck defects, especially defects which need osseous reconstruction. VSP encompasses computer aided design/computer assisted manufacturing (CAD/CAM) and creation of defect-specific 3D-printed models. The main advantage of VSP lies in the creation of patient-specific reconstructive materials including premade osteotomy guides and prefabricated titanium plates. Studies have shown shortened operative time and ischemia time when VSP is compared to traditional free-hand reconstruction [69]. In a study by Chang et al. there was a significant reduction in operative time in patient who underwent VSP versus those who did not get a VSP (545 min vs. 666 min, $p < 0.005$), respectively [70]. Barr et al. reported reduction in operative time by 44.64 min (95% confidence interval [CI] − 74.69 to − 14.58 min; $P < 0.01$) [71]. The same study also reported a trend toward shorter hospital stay (mean difference − 1.24 days, 95% CI − 4.00 to 1.52 days; $P = 0.38$). VSP has also been shown to improve accuracy, especially in cases which need two or more osteotomies [72]. VSP has a high reproducibility and reduces osteotomy errors as measured by multiple osteotomies and repeated burring [72, 73].

Barriers to routine use of VSP include increased costs and delays in device manufacturing. Additionally, there is always a chance of change on resection plans based on intraoperative modifications. Costs can be reduced by developing in-house 3D-printing systems instead of commercially available vendors [73, 74]. Studies have also shown comparable complication rates with and without the use of VSP [72]. Despite these barriers and lack of randomized controlled trials, VSP-guided osseous reconstruction for oral cavity defects is increasing in popularity. However, at this time the authors recommend utilizing VSP on a case-by-case basis depending on the needs of the head and neck reconstruction.

Sentinel Node Biopsy

Sentinel lymph node biopsy (SLNB) is traditionally reserved for the detection of occult lymph node metastases in early stage OSCC which can be transorally resected without opening the neck for resection of the primary tumor or reconstruction [75]. A large retrospective study, a recent systematic review and meta-analysis, and two prospective randomized trials have shown a similar locoregional free, disease-specific and overall survival for SLNB versus elective neck dissection in patients with early stage OSCC [72–78]. However, an application of SLNB in LAOCSCC may be staging of the contralateral neck regardless of the presence of ipsilateral metastases. In patients with OSCC an incidence of contralateral lymph node metastasis up to 36% has been reported [78]. Risk factors are tumors arising in the floor of mouth, tumors crossing the midline, advanced staging (cT3–4), primary tumor more than 3.75 mm thick, and multiple ipsilateral node involvement [79, 80]. The rate of contralateral metastasis in a recent pilot study investigating the role of SLNB in well-lateralized LAOCSCC was 5% [81]. Authors hypothesized tailoring the treatment of the contralateral neck based on the results of the SLNB. The main limitation of SLNB in LAOCSCC is the accessibility for peri-tumorally tracer injections. Currently the role of SLNB in the management of LAOCSCC is not well defined because of the limited data. Large-scale studies are warranted to outline the utility of SLNB in LAOCSCC. Table 2 summarizes the components that should be considered in management algorithms of all patients with LAOCSCC during discussion in a multidisciplinary setting.

Table 2 Components of a management algorithm in locally advanced oral cavity squamous cell carcinoma (LAOCSCC)

Determinants	Modalities
Operability	Clinical examination
	CECT
	MRI
Metastatic workup	PET/CT
Surgical excision with margins	Intraoperative assessment of surgical margins
	Frozen section (most commonly used)
	Image guided (US/MRI/PET/targeted fluorescence imaging)
	3D anatomical specimen digital modeling
Management of the neck	Neck dissection
	SLNB (limited role in LAOCSCC)
Reconstruction	Free flaps (preferred) with or without VSP (for bony reconstruction)
	Regional flaps
Adjuvant therapy	Radiation therapy with or without chemotherapy

CECT contrast-enhanced computed tomography, *MRI* magnetic resonance imaging, *PET/CT* positron emission tomography/computed tomography, *US* ultrasound, *SLNB* sentinel lymph node biopsy, *LAOCSCC* locally advanced oral cavity squamous cell carcinoma, *VSP* virtual surgical planning

NON-SURGICAL STRATEGIES: RADIATION THERAPY/ CHEMOTHERAPY

Primary Radiation Therapy and Chemotherapy

For LAOCSCC, the role of surgery has been well established in literature from the past several decades, as already discussed above. This is based mostly on retrospective cohort studies and population-based studies demonstrating inferior outcomes with non-surgical management. Results of an NCDB study showed that patients undergoing surgery followed by RT versus patients undergoing CRT had a 3-year survival of 53.9% and 37.8%, respectively (CI 13.6–18.6%) [82]. Cannon et al. performed a retrospective population database study using the Surveillance, Epidemiology, and End Results (SEER) database of 5856 patients from 1988 to 2008 and showed reduced OS and DFS and a trend of increasing usage of non-surgical therapy for advanced stage oral cavity cancer [83]. Prospective data are somewhat limited but have also suggested similar inferiority with primary CRT compared to primary surgery [2]. The 10-year update and subset analysis of a randomized trial comparing surgery and adjuvant RT versus concurrent CRT in patients with advanced, non-metastatic squamous cell carcinoma of the head and neck showed a better DFS in the surgery arm versus the chemoradiation arm (68% vs. 12%, $p = 0.038$) [84]. Forner et al. reported that definitive RT/CRT significantly increased the hazard of death compared to primary surgery (HR 2.39, 95% CI 1.56–3.67; $I^2 = 63\%$) [85].

Foster et al. described a retrospective series of 140 patients with LAOCSCC treated over a 20-year period with primary CRT [86]. Overall, they demonstrated 5-year OS (63.2%), progression-free survival (58.5), and locoregional control (78.6%) [86]. Hosni et al. recently captured a retrospective cohort with similar outcomes [87]. They identified 108 patients who underwent non-operative management for OCSCC due to a variety of reasons (medically unfit, unresectable disease, patient refusal of surgery, extensive oropharyngeal involvement, attempted preservation of oral structure/function) with 5-year OS of 50%, cancer-specific survival of 76%, and DFS of 42% [87].

One of the main reasons that oral cavity cancer is less favorable for primary RT compared to other sites, such as the oropharynx, is that the mandible is in extremely close proximity. Osteoradionecrosis (ORN) of the mandible is a consideration any time radiation is administered to the oral cavity. Rates of ORN in current literature are variable, with published studies suggesting this is between 6% and 36% for primary CRT [86–91]. Even large segmental defects of the mandible can be replaced with excellent functional and cosmetic outcomes, thanks in large part to osseous autologous microvascular reconstructive techniques. However, such surgeries do still carry an inherent amount of morbidity. Modern RT techniques (i.e., intensity-modulated radiation therapy) have likely improved the risk of ORN with primary RT compared to more traditional data, but this remains a real consideration. Moreover, the increasing availability of RT with protons and heavy ions promises better sparing of healthy tissues around the tumor, including the mandible bone, and, especially in the case of heavy ions, greater efficiency compared to conventional photon-based radiotherapy, in adjuvant and re-irradiation settings [92, 93].

Neoadjuvant Chemotherapy/Immunotherapy

Neoadjuvant treatment has not gained an established role in the management of OCSCC. Overall, neoadjuvant chemotherapy has not been shown to have any major benefit over primary surgery. Kende et al. recently performed a systematic review on neoadjuvant chemotherapy for oral cavity cancer [94]. They identified 1373 patients from eight studies (three randomized controlled trials, five retrospective studies) showing no obvious difference in survival outcomes when comparing neoadjuvant chemotherapy to upfront surgery, despite identifying a reduced risk of margin positivity in the neoadjuvant chemotherapy group ($P = 0.007$) [94].

Neoadjuvant chemotherapy has been suggested as a possible strategy for mandibular preservation in resectable oral cavity cancer. Chaukar et al. performed a phase II prospective study for T2–T4, N0/1 OCSCC and compared surgery and adjuvant therapy to neoadjuvant chemotherapy followed by surgery ($n = 68$) [9]. Mandibular preservation rate was 47% in the neoadjuvant group with a comparable median DFS and OS. Licitra et al. performed a prospective randomized study of resectable T2–T4, N0–N2 OCSCC comparing neoadjuvant cisplatin and fluorouracil followed by surgery compared to upfront surgery [95]. Overall, no survival benefit was seen (5-year OS 55% for both arms) but 31% of patients in the neoadjuvant arm underwent a mandible resection, compared to 52% in the primary surgery arm [95]. Recently, Abdelmeguid et al. reported on retrospective series of 120 patients with LAOCSCC (stage IV, 79%) who received two cycles of neoadjuvant chemotherapy. Of 76 (63%) patients with at least partial response to chemotherapy, 60 underwent surgery: 15 had less extensive surgery than originally planned with organ preservation achieved in 41% of those with favorable response to neoadjuvant chemotherapy. Responders to neoadjuvant chemotherapy had better 5-year OS (60% vs. 34%) and disease-specific survival (78% vs. 46%) than non-responders [96]. Similarly, Gangopadhyay et al. reported that the resectability rate in T4b tumors following neoadjuvant chemotherapy was about 36% and the resectability rate was better when the disease was infranotch versus supranotch ($p < 0.000$) on multivariate analysis. However, there was no survival difference between the two groups.(3-year OS was 44.2% and 48.2%, respectively; $P = 0.932$) [97].

The role of neoadjuvant immunotherapy is an emerging topic that remains incompletely defined for OSCC. Neoadjuvant immunotherapy has gained some traction in other non-oral cavity disease sites, with recent studies suggesting favorable outcomes with neoadjuvant immunotherapy in resectable cutaneous squamous cell carcinoma and melanoma [98, 99]. The application of immunotherapy in the neoadjuvant setting does have some appeal in comparison to chemotherapy. The possibility of shorter neoadjuvant regimens might allow for minimal or no delay in surgery. There has been a specific concern that neoadjuvant immunotherapy may increase the risk of poor wound healing and postoperative complications following surgery [100]. Tang et al. published a retrospective analysis of patients with LAOCSCC (n = 64) who received neoadjuvant pembrolizumab, with no difference in wound healing or complications (lymphedema, trismus, return to operating room, infection, fistula, wound dehiscence, flap failure, or hematoma) compared to a matched control cohort who did not receive neoadjuvant immunotherapy [101]. Schoenfeld et al. performed a randomized prospective phase 2 clinical trial in which patients with untreated OSCC (T $\geq$ 2 or clinically node positive) were randomized to receive nivolumab (two cycles, n = 14) versus nivolumab + ipilimumab (one cycle, n = 15) followed by definitive surgery [102]. All recruited patients were able to get neoadjuvant therapy without any delay in initiation of surgery. The 1-year progression-free survival was 85% and 1-year OS was 89%. This study showed a volumetric response in 50% of patients in the nivolumab arm and 53% of patients in the nivolumab + ipilimumab arm. Knochelmann et al. performed a single-arm phase 2 trial with 12 patients who received 3–4 doses of biweekly neoadjuvant nivolumab [103]. They showed an overall response rate of 33% and a relatively good safety profile.

QUALITY OF LIFE ISSUES

Surgery for LAOCSCC can have some serious consequences for patients in terms of not just oncologic and functional outcomes but also psychological implications like higher depression scores [104]. Using five questionnaires, namely tumor-specific QoL (European Organization for Research and Treatment Cancer Quality of Life Questionnaire—Head and Neck Cancer, EORTC-QLQ-HN43); severity anxiety/depression (Hospital Anxiety and Depression Scale, HADS); participation (Impact on Participation and Autonomy, IPA); supportive care needs (Supportive Care Needs Survey Short-Form 34, SCNS-SF34), and the FACE-Q Head and Neck Cancer Module, Douglas et al. reported that age, length of stay and surgery, time since operation, Comorbidity Index, and 10-year OS were associated with quality of life (QoL) outcomes. Studies have shown that a patient's loss of a sense of well-being and reduced QoL also negatively affect survival [105, 106]. Poor QoL scores are associated with higher mortality [105]. A trial by Basch et al. found that patient-reported outcomes (PRO) for symptom monitoring during cancer treatment improved OS of patients on the PRO arm than in the usual care pathway arm: 31.2 months (95% CI 24.5–39.6) vs. 26.0 months (95% CI 22.1–30.9), respectively [107]. Early symptom reporting helped the healthcare providers prevent downstream adverse events. Psychological distress has been shown to be another consideration in long-term QoL [108]. Thus, it is of paramount importance that psychological support be included in the care pathways of these patients, making a multidisciplinary team approach to the management of these patients—preferably at a high-volume center—invaluable [109].

CONCLUSION

The general consensus clearly is that surgery remains the preferred primary treatment modality for LAOCSCC in the current era. T4b OCSCC is a heterogenous group and larger studies to further stratify these patients may be justified. Recent evidence has shown that there is a high rate of downstaging of T4b disease to T4a following surgery. Thus, it is prudent to say that surgery should be offered to patients even with T4b disease, if it is an option. However, consideration can be made for primary CRT in patients who are either unable or unwilling to get surgery. Neoadjuvant chemotherapy has not gained significant traction; further studies are needed to define its role as an organ-preservation strategy. Neoadjuvant immunotherapy is a treatment modality with potentially even more appeal but requires further investigation. A high-volume multidisciplinary team, experienced oncologic and reconstructive surgeons, and a sound understanding of the disease processes and complex anatomy and function of the oral cavity are crucial. Evidence-based management of LAOCSCC should be prioritized by taking into consideration QoL expectations of individual patients.

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Declarations

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