Current Oncology Reports (2019) 21:99
https://doi.org/10.1007/s11912-019-0845-8

HEAD AND NECK CANCERS (EY HANNA, SECTION EDITOR)

Contemporary Approach to Locally Advanced Oral Cavity Squamous Cell Carcinoma

Christopher M. K. L. Yao[1] · Edward I. Chang[2] · Stephen Y. Lai[1]

Abstract

Purpose of Review Surgical management of locally advanced oral cavity squamous cell carcinomas (OCSCC) has long been recognized as a primary treatment modality. Technological advances have led to significant improvements in our surgical approach, from improvement in the visualization of tumors to more efficient and precise reconstruction. Here, we review the latest technological advances in surgical extirpation and reconstruction of locally advanced OCSCCs.

Recent Findings The focus of technological innovation in surgical extirpation has been on improving visualization, with the use of intraoperative ultrasound for margin delineation, intraoperative navigation, narrow-band imaging, and the use of fluorescence. Though early, these are promising steps to ensuring complete resection of the cancer. Advances in reconstruction have been centered on the incorporation of computer assisted design, manufacturing, and virtual surgical planning, allowing for more complex three-dimensional defects to be expeditiously reconstructed.

Summary As these technologies are still under development, their impact on oncologic outcomes are not yet robustly defined; however, as technology continues to advance and become more widely available, new technologies will undoubtedly become integrated into enhancing surgical precision and planning.

Keywords Advanced oral cavity carcinoma · Oral cavity reconstruction · Technology · Tumor margins · Image-guided surgery · Virtual surgical planning

Introduction

Oral cavity cancer remains one of the most common malignancies of the head and neck, and the 15th most frequent form of cancer in the world, with an estimated 200, 000 new worldwide each year (http://globocan.iarc.fr/Pages/fact_sheets_population.aspx). Tobacco and alcohol remain the major culprits with a well-documented synergistic effect, although areca and betel nut chewing, poor dental hygiene, chronic trauma, as well as genetic susceptibility may also play etiologic roles. Overall, 90% of oral cavity cancers are squamous cell carcinomas (OCSCCs).

OCSCCs arise from the epithelial mucosa of the oral cavity. The oral cavity is bounded by the skin-vermillion lip junction anteriorly, extending to the hard-soft palate junction superiorly and the circumvallate papillae of the tongue posteriorly. There are eight distinct subsites including the oral anterior 2/3 of the tongue, mucosal lip, floor of mouth, gingiva covering the upper and lower alveolar ridge, retromolar trigone, hard palate and buccal mucosa. OCSCCs from all subsites not only have a tendency to invade locally, but also spread to the cervical lymphatics as well. Up to 45% of patients harbor metastases to cervical lymph nodes at presentation [1].

The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) classify OCSCCs based on the tumor, node, metastases (TNM) system (Table 1). By definition, locally advanced oral cavity cancers

This article is part of the Topical Collection on *Head and Neck Cancers*

✉ Christopher M. K. L. Yao
cmyao@mdanderson.org

✉ Edward I. Chang
eichang@mdanderson.org

✉ Stephen Y. Lai
sylai@mdanderson.org

[1] Department of Head and Neck Surgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd. Unit 1445, Houston, TX 77030, USA

[2] Department of Plastic Surgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd. Unit 1258, Houston, TX 77030, USA

Published online: 07 November 2019

Table 1 American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) 8th Edition Clinical TNM staging criteria for Oral Cavity Squamous Cell Carcinomas

	Criteria
T Stage	
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm AND DOI ≤ 5 mm
T2	Tumor larger than 2 cm but ≤4 cm AND DOI ≤ 10 mm, or
	Tumor ≤2 cm with DOI > 5 mm but ≤10 mm
T3	Tumor larger than 4 cm, or
	DOI > 10 mm
T4a	Mucosal Lip: involvement of cortical bone, inferior alveolar nerve, floor of mouth, skin of face
	Oral Cavity: cortical bone of maxilla/mandible, maxillary sinus or skin of face
T4b	Involves masticator space, pterygoids, skull base or encases carotids
N Stage	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis identified
N1	Single ipsilateral node measuring 3 cm or smaller, without ENE
N2a	Single ipsilateral node larger than 3 cm but less than 6 cm, without ENE
N2b	Multiple ipsilateral nodes, all less than 6 cm, without ENE
N2c	Contralateral or bilateral node(s), all less than 6 cm, without ENE
N3a	Any node larger than 6 cm, without ENE
N3b	Any node(s) with clinically overt ENE (ENE)
M Stage	
M0	No distant metastasis
M1	Distant metastasis

DOI – Depth of Invasion, ENE – Extranodal Extension

are: (i) greater than 4 cm in greatest dimension, (ii) have a depth of invasion greater than 1.0 cm, or (iii) invade nearby structures. For mucosal lip cancers, this includes invasion of cortical bone, inferior alveolar nerve, skin of face or floor of mouth. For other oral cavity subsites, this includes invasion through the cortical bone of the mandible, maxilla, maxillary sinus, or skin of face. Invasion of the masticator space, pterygoids, skull base or encasement of the carotid artery is generally considered unresectable in terms of achieving complete surgical clearance of disease, although resectability has been challenged in tumors with extension up to the mandibular notch [2, 3].

Over the last forty years, developments and improvements in diagnostic imaging, surgical techniques, radiation therapy, and a more nuanced understanding of systemic agents and rehabilitation therapies have led to a steady improvement in the overall survival of oral cavity cancers [4]. Overall survival has improved for early-stage disease from a three-year survival of 78.0% (SE = 1.3) in 1973–1980 to 92.2% (SE = 1.1) in 2011–14. While in late-stage disease, the three-year survival has improved from a three-year survival of 51.9% (SE = 1.5) in 1973–80 to 70.3% (SE = 1.9) in 2011–14. Over this period of time, the treatment paradigm has largely remained unchanged, with surgery playing a primary role in prognostication and definitive treatment. Discussion of the surgical management of the neck is beyond the scope of this review, however, the cervical nodal basins may also require management, particularly for locally advanced tumors, or clinically evident nodal disease. Finally, another critical consideration in surgical planning is the likelihood for patients to require adjuvant therapy in the forms of radiation or chemoradiation. In these cases, it is prudent to optimize surgical technique and wound healing to minimize delays in receiving adjuvant therapy [5].

With surgery, technological advancements have progressed over the last decade with significant strides made in the use of computer-assisted surgical planning and reconstruction [6]. Technological advances in tumor resection are equally important and have been focused on improving visualization of the tumor, minimizing positive surgical margins, and enhancement of surgical precision. Here, we will review the technological advances in planning both surgical extirpation and reconstruction.

Principles of Surgical Extirpation

Surgical excision remains the primary modality for treatment of locally advanced OCSCCs. A critical goal of surgery is to achieve clear oncologic margins, since residual disease is fraught with worse overall survival and necessitates adjuvant therapy in the form of radiation, chemotherapy, or both. The oncologic clearance of disease becomes further highlighted in locally advanced tumors, whereby patients often have to undergo lengthy, potentially functionally debilitating and disfiguring surgery.

In the surgical planning process, knowing the three-dimensional location of the tumor relative to anatomical structures, and the propensity for which tumors can invade is paramount. Each subsite of the oral cavity has unique properties and knowing the extent of the tumor invasion can at times be difficult.

Oral tongue cancers typically arise from the lateral border, and occasionally the ventral surface. As they progress, they typically invade the extrinsic muscles of the tongue, but can also extend into the sublingual space and cross the midline. When the floor of mouth is involved, the mandible is at risk of erosion and invasion. Tongue cancers can also spread posteriorly towards the base of tongue, vallecula, and pre-epiglottic space, where the retromolar trigone and lateral oropharyngeal wall become at risk. Gingival, buccal and lip cancers all have the ability to erode the mandible, maxilla, and externally towards the facial skin. Advanced gingivo-buccal cancers can become particular hard to treat when they spread posteriorly towards the retromolar trigone and masticator space. Once a tumor reaches the retromolar trigone, it has the ability to spread in multiple directions, including superiorly along the pterygomandibular raphe towards the hard palate, masticator space, pterygopalatine fossa; posteriorly towards the vertical ramus of the mandible, or tonsil; anteriorly along the buccal mucosa, inferiorly along the floor of mouth and base of tongue. Cancers of the hard palate may progress towards the nasal vault, maxillary sinus, and through the greater palatine foramen and canal into the pterygopalatine fossa.

Currently, the extent of surgical excision is determined by a combination of (1) conventional cross-sectional imaging modalities such as CT and MR imaging, (2) palpation and subtle visual observations to delineate where abnormal tissue ends and normal tissue begins, and (3) the use of frozen section pathology analysis for the presence of subclinical disease at the margin. With these technologies, a recent study based on the National Cancer Data Base (NCDB) from 1998 to 2012 found a pooled positive tumor margin rate for oral cavity cancers of 12.75% [4], consistent with single institution study rates of 1–22% [7–12]. Positive surgical margins have significant prognostic implications with increased rates of locoregional recurrence and decreased overall survival, highlighting the importance of complete oncologic extirpation [13].

Contemporary Techniques in Ablative Surgery

There are many nuances in translating cross-sectional imaging modalities to the surgical field and ensuring surgical precision. Importantly, the timing of preoperative imaging has relevance to progression of disease. Regardless, critical features to evaluate during surgical planning include mandibular or bony cortical erosion, extent of soft tissue invasion, invasion towards the masticator space, perineural spread, tumor thickness, and nodal evaluation.

The decision to perform a segmental mandibulectomy relies on accurate preoperative imaging. Significant cortical erosion and frank invasion of the inferior alveolar nerve are clear indications; however, in cases of edentulous, irradiated mandibles or a large, bulky tumor, a segmental mandibulectomy should be considered as well [14]. The presence of mandibular invasion cannot reliably be identified by clinical examination alone. SPECT bone imaging provides the greatest sensitivity for mandibular invasion (100%), but suffers from poor specificity (29%) [15]. Mukherji et al., demonstrated that a conventional CT scan with 3 mm sections in bone and soft-tissue algorithms had a high sensitivity (96%) and specificity (87%) for mandibular invasion [16], although a recent meta-analysis found a pooled sensitivity of (72%) and specificity of (90%) [17]. The same investigators also published a meta-analysis on using magnetic resonance imaging (MRI) in determining mandibular invasion and found a pooled sensitivity of 78% and specificity of 83% [18]. Although generally considered satisfactory, the main challenge for the diminished sensitivity and specificity of these imaging modalities is failure to assess the alveolar crest in the presence of coexisting odontogenic infection or artifact. Most recently, a new generation of multidetector CT (MDCT) scanners with the ability to provide sections as thin as 0.625 or 0.75 mm have raised sensitivity and specificity levels to 94% and 90% respectively [19].

OCSCCs may present with perineural invasion at initial work-up in 5–10% of patients. This is depicted in CT imaging as loss of normal fat density, excessive enhancement of the nerve, bony foraminal widening or erosion; and can similarly be identified by MRI, whereby superior visualization and leakage of contrast agent in the blood-nerve barrier can be visualized as nerve enhancement before nerve enlargement. Although the sensitivity of MRI for perineural spread has been found to be as high as 95% [20–22], Imaizumi et al. cautioned that there can be an overestimation of perineural invasion by MRI scans due to surrounding inflammation [23]. Visualizing tumor thickness may be limited by the inability of static MRI or CT imaging to distinguish between exophytic and deeply invasive, endophytic tumors in a closed mouth. In thicker tumors, there is better correlation between the MRI measured thickness and the histological thickness oral tongue cancer [24].

Overall, a recent review suggested a contrast-enhanced 16 section MDCT is preferred when evaluation of bony erosion is critical such as in gingival, buccal, or lip subsites of OCSCCs. Alternatively, where soft-tissue resolution is more important in surgical planning, such as in oral tongue and floor of mouth cancers, contrast-enhanced MRI may be preferred [25].

When planning surgery, careful visualizing and mapping of not only the primary tumor lesion, but also the surgical margin is critical. In particular, with different oral cavity cancer subsites, there is at least a 20–30% anticipated shrinkage of tissue upon extirpation [26, 27]. For oral tongue cancers, a 1–2 cm surgical margin around from the edge of the tumor in all directions is recommended where feasible and should achieve a resection margin of 5 mm [28–30]. For floor of mouth cancers, a planned 1 cm margin is often needed, and the deep margin may require resection and excision of sublingual glands, mandibular periosteum, a marginal or even a segmental mandibulectomy in order to achieve an adequate margin [31]. In buccal mucosa cancers, achieving a deep margin is complicated by native anatomy, whereby the thickness between the buccal mucosa to external skin approaches a thickness of 1.5 cm. As such, if the invasion and edge of the tumor is less than 1.3 cm from the external skin, it may be possible to preserve the external skin while capturing the intervening mucosa, fatty layer, and muscular layer [32]. However, potential sacrifice of one or more branches of the facial nerve may be necessary. Another method of determining the thickness of the deep margin may involve the use of ultrasound in determining which structures have been invaded [33]. For planning bony margins, this has traditionally been determined based on imaging analyses given the challenge of high mineral content and need for decalcification to assess bony pathology specimens. Available strategies to confirm a clear surgical bony margin include frozen section pathologic analysis of curettaged cancellous bone, bone marrow scrapings, and cryostat sections with excellent correlation with final pathologic diagnosis [34–37]. The NCCN guidelines describe an "adequate" margin with a clear margin defined as ≥5 mm, a close margin being <5 mm from the invasive tumor and a positive margin as either having invasive carcinoma or carcinoma-in-situ at the margin [38]. This distinction may vary depending on anatomic subsites.

Finally, although highly sensitive, intraoperative frozen section can be time consuming, and offer false assurance as only a small portion of the wound bed or margin is sampled [39]. The adequacy of the portion sampled does vary by technique (*from specimen* vs. *tumor bed)* and orientation (perpendicular, or parallel *en-face),* but regardless of the selected method must be communicated well between the pathologist and surgeon. To address all these challenges, there have been several promising developments including intraoperative oncologic imaging, wide-field optical imaging techniques, and the addition of fluorescent contrast imaging.

Emerging Techniques in Ablative Surgery

Intraoperative Ultrasound

With complex soft tissue resection of the oral cavity, ultrasound has emerged as an additional tool that can be used to better predict the depth of invasion. Ultrasound can be used to map a 1.0 cm gross deep clearance, and interrogate the final resected specimen for adequacy of surgical margins [40•, 41, 42]. Utilizing a braided suture or needle to map out the ultrasound-determined deep margin has also been described to provide better assurance of the adequacy of the deep margin. The use of intraoperative ultrasound, though effective, has not yet been correlated with histologic findings, may be associated with prolonged operative time, and does depend on the skill and experience of the user.

Intraoperative Navigation

The use of image guidance and navigation systems has been seamlessly incorporated into neurosurgical and skull base surgeries, greatly enhancing the precision and quality of surgery. When fused with a planning software, image guidance systems can be combined with software to virtually plan the resection, including contouring the tumor and defining the margin of resection with the positioning of "landmarks" within the software. Cantazaro et al. found that implementing virtual planned surgery resulted in wider margins and improved orientation with their pathologists [43]. Another study demonstrated shorter operative times and fewer complications with computer-assisted surgeries [44]. The challenge remains in using intraoperative navigation to map soft tissue structures, however, some studies have started to evaluate how surgical positioning may affect the soft tissue position [45]. Furthermore, to circumvent the delay between preoperative imaging and the operating room, some hospitals equipped with intraoperative Cone Beam CT scanners have also incorporated the imaging study into their workflow [46].

Narrow Band Imaging

Narrow Band Imaging (NBI) is a newer video endoscopic system with narrow band filters that allow for the passage of only two specific wavelengths of visible light, corresponding to the absorption peaks of hemoglobin. This filtering allows for enhanced visualization of microvascular changes that can occur within the mucosal surface during carcinogenesis, specifically at the level of the intraepithelial papillary capillary loop (IPCL), located just below the epithelial basement membrane. During carcinogenesis, the IPCL may exhibit changes including: dilatation, meandering, caliber change, and non-uniformity. The patterns seen on NBI have been classified into a system (Table 2), whereby a type III finding (IPCL

Table 2 Classification of Oral Squamous Epithelium by NBI Findings

NBI Findings	*Criteria*
Type 1	Normal mucosa, regular brown dots
Type II	IPCL pattern dilation and crossing
Type III	IPCL pattern elongation and meandering
Type IV	IPCL pattern destruction and angiogenesis

IPCL = intraepithelial papillary capillary loop

pattern elongation and meandering) had a 84.62% sensitivity and a 94.56% specificity at detecting carcinoma in oral leukoplakia [47].

Given the enhanced visualization of abnormal mucosa, there has been significant interest in applying this technology in the operation room. Tirelli et al. found a decrease in their positive superficial margin rates, and improved detection of dysplasia and cancer around the primary specimen when using narrow band imaging technology compared with white light [48]. By improving our visualization of subtle mucosal changes, NBI is a promising development that may aid in surgical planning and improving margin assessment.

Optical Advances in Surgical Visualization

Highlighting the lesion of interest with fluorescence offers another strategy to improve visualization. The tumor's own fluorescence signature has been assessed as a possible method in distinguishing tumor cells from normal cells. However, the sensitivity and specificity of autofluorescence was found to be insufficient for accurate delineation of cancers. As such, there has been significant strides in developing exogenous agents that could potentially target the tumor and allow for better intraoperative visualization. The epidermal growth factor receptor (EGFR), a tumor-membrane bound biomarker has been leveraged and when targeted with a peptide bound to a fluorescent agent, can increase the specificity of these fluorescent agents to sub-millimeter resolution. These agents allow for robust fluorescent tumor-to-normal-tissue signal in real-time. The majority of patients tolerated the fluorescent agents well, although some may also experience adverse reactions (e.g., rash) similar to unlabeled cetuximab [49, 50••]. Furthermore, to account for tumor heterogeneity, a cocktail of receptor targeting agents could be used to increase the tumor to background ratio. Beyond use of a fluorescent marker, researchers have found that using near-infrared wavelengths with special photodetector cameras allow for deeper tissue penetration, reduced light scattering, and superior sensitivity compared with preoperative imaging [51–53]. Currently, there are more peptides and targeting agents undergoing evaluation, including those that aim to target critical structures such as nerves [54, 55]. Other novel imaging modalities, such as the Raman spectroscopy, which captures the photon scattering pattern to distinguish cancer from healthy tissue are undergoing active investigation. However, their investigation has been mostly in non-head and neck cancers [56, 57].

Deep Learning

Convolutional neural network (CNN) is a type of machine learning that can be used to enhance pattern-recognition whereby unannotated raw images can be uploaded and classified based on a large dataset of pre-classified images. As these algorithms become more efficient and sophisticated, this technology may eventually be capable of guiding surgeons intraoperatively in real-time and assist with recognizing different structures. Most recently, CNN has been applied to a clinic setting, whereby it was found to identify high risk regions in video sequences of OCSCCs, with immediate biopsy and histologic evaluation revealing an accuracy of 88.3% [58••].

Contemporary Head and Neck Reconstruction

Reconstruction of complex head and neck defects following cancer extirpation presents unique challenges to the reconstructive surgeon who is charged with reconstructing a 3-dimensional defect in order to restore both form and function. Shaping and contouring a bone flap that needs to be secured to the remaining craniofacial skeleton with titanium plates, while simultaneously manipulating a soft tissue flap can be extremely difficult. When taking into consideration the need to optimize post-operative speaking and swallowing function, restore dental occlusion or prepare for dental rehabilitation, and achieving the best overall esthetic result, the reconstruction can be quite cumbersome, time consuming, and often resulted in suboptimal outcomes, particularly when patients presented with significant deformities and extensive disease.

Increasingly, the integration of virtual surgical planning (VSP), rapid prototyping with three-dimensional printing technologies, computer-assisted design and manufacturing (CAD-CAM) are being integrated into reconstructing complex head and neck defects (Fig. 1 This technology can optimize segmental mandibulectomy and maxillectomy defects with vascularized osseous and osteocutaneous free tissue transfers by precisely calculating the precise angles, and lengths of osteotomies that would restore the patient's preoperative anatomy and architecture. However, the technology is not only valuable in planning the reconstruction, but is also closely coupled to the resection where guides are engineered for the tumor extirpation as well. Presently, preoperative imaging can be integrated with computer software to allow for VSPs and the manufacturing of patient-specific cutting guides and reconstruction plates. Virtual planning involves the ablative surgeon, reconstructive surgeon and a biomedical

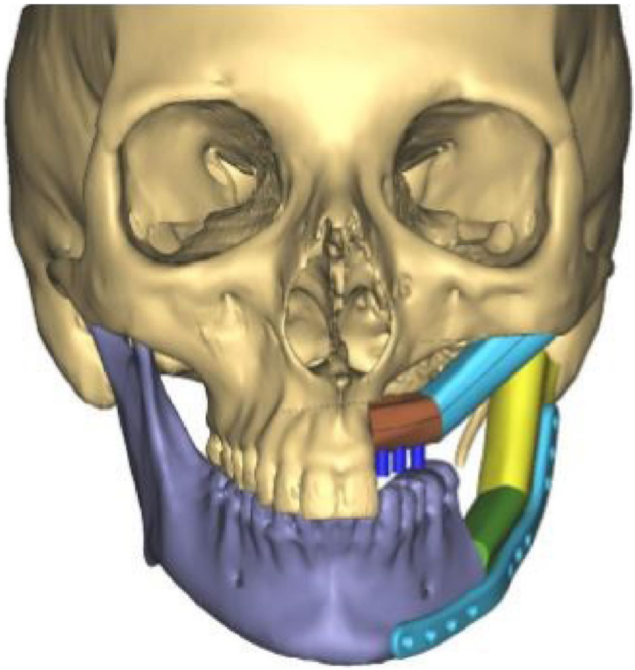

Fig. 1 Example of a virtual plan with the mandibular and maxillary defect and reconstruction with a left fibula graft using computer-assisted design, manufactured precise cutting guides, and patient specific plate

engineer discussing the specific location of the recipient and donor osteotomies, the vascular pedicle position and the sidedness of the donor site. This includes discussion of the specific details of the patient-specific reconstruction plate, plate thickness, length of plate, screw positions, distance between screws and angulation of screws. Although not necessary, incorporating patient-specific donor site imaging and computer tomographic angiography also allows for the precise placement of donor cutting guides around perforators, minimizing any intraoperative modification of the virtual plan [59]. One of the main challenges with the use of virtual planning are intraoperative modifications. Changes to the surgical plan may place the entire reconstruction into misalignment, and although this can occasionally be accommodated with some intraoperative adjustments, reduction in bone-to-bone contact surface area may compromise the ability for bony fusion.

During the resection, preplanned cutting guides are attached to the native mandible or maxilla with screws, with the guide allowing for exact osteotomies. These cutting guides typically have preplanned drills holes that correspond with the reconstruction plate and bony free flap. Furthermore, rapid prototyping vendors provide models of the mandible, maxilla, in addition to milling patient-specific reconstruction plates. Although plates can also be bent based on a stereolithographic model with equivalent accuracy to patient-specific plates, any manipulation of a plate has the potential of introducing weakened areas [60•]. Whether this leads to premature hardware failure remains to be determined.

Overall, the advantages of virtual planning, and incorporating CAD-CAM technology include reduced operative time, reduced flap harvest and ischemia time, and the ability to perform more complex reconstructions involving multiple bony segments and osteotomies [61–63]. In fact, Chang et al. found a decrease in operative time from (666 min to 545 min; $p < 0.005$) in a total of 92 patients undergoing mandibular reconstruction with the incorporation of VSP, and a decrease in bony nonunion as well [64••]. This is particularly important as many of these patients will require subsequent adjuvant radiation, which may impact bony healing.

A critical consideration with use of VSP, is the timing of the preoperative scan. Vendors typically recommend scans no older than 3 months; however, in the setting of rapidly growing tumors, or with the use of neoadjuvant therapy, more recent imaging, within 6 weeks of the surgery date may allow for more accurate planning. To overcome tumor progression from the preoperative imaging and minimize intraoperative improvisation, several strategies have been devised, including the use of "triple-cut" cutting guides for both the recipient and donor sites, to allow for progressive wider margins [65], and automated software algorithms that automate the design of bony reconstructions [66].

One additional feature that is often considered the gold-standard in rehabilitative reconstruction is the implementation of dental implants [67]. Although there is controversy regarding the timing of implant placement relative to radiotherapy and the exact technique to minimize free flap complications, a relatively low percentage of reconstructed patients eventually go on to complete prosthestic dental rehabilitation [68, 69]. The low rates of dental rehabilitation may in part be due to the cost of dental implants, dentures, and prosthodontics, along with the risk of developing osteoradionecrosis of either the donor or native bone following implant placement into radiated bone (7.7%) [70]. However, it has been found that 80% of patients that do go on to seek dental rehabilitation achieve full dental restoration. Techniques to increase the likelihood of successful osseointegrated implants in fibular free flaps are also being developed, including the use of morselized bone from adjacent native bone to increase bone density and decrease free flap complication rates [71, 72]. Furthermore, computer-assisted surgical plans have allowed for a single stage operation to incorporate dental implantation at the time of reconstruction with excellent efficacy [73].

Conclusion

Surgery remains a critical modality in the management of advanced oral cavity squamous cell cancers. Significant strides in technology are rapidly being developed to enhance surgical precision. Advances in imaging technology, intraoperative localization, and fluorescent technology can aid in better visualization of the tumor and subsequent extirpation with adequate margins. Virtual surgical planning and advances in computer software offer the potential for significant improvements in the efficiency, accuracy, and precision of surgical reconstruction.

Compliance with Ethical Standards

Conflict of Interest Christopher M.K.L. Yao declares that he has no conflict of interest.

Edward I. Chang declares that he has no conflict of interest.

Stephen Y. Lai has received compensation from Cardinal Health for service as a consultant.

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.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Ow TJ, Myes JN. Current management of advanced resectable oral cavity squamous cell carcinoma. Clin Exp Otorhinolaryngol. 2011;4:1–10.
2. Liao CT, Ng SH, Chang JT, Wang HM, Hsueh C, Lee LY, et al. T4b oral cavity cancer below the mandibular notch is resectable with a favorable outcome. Oral Oncol. 2007;43(6):570–9.
3. Liao CT, Lee LY, Hsueh C, Lin CY, Fan KH, Wang HM, et al. Comparative outcomes in oral cavity cancer with resected pT4a and pT4b. Oral Oncol. 2013;49(3):230–6.
4. Cheraghlou S, Schettino A, Zogg CK, Judson BL. Changing prognosis of oral cancer: an analysis of survival and treatment between 1973 and 2014. Laryngoscope. 2018;128(12):2762–9.
5. Huang SH, O'Sullivan B. Oral cancer: current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir Bucal. 2013;18(2):e233–40.
6. Kraeima J, Schepers RH, van Ooijen PMA, Steenbakkers RJHM, Roodenburg JLN, Witjes MJH. Integration of oncologic margins in three-dimensional virtual planning for head and neck surgery, including a validation of the software pathway. J Craniomaxillofac Surg. 2015;43(8):1374–9.
7. Orosco RK, Tapia VJ, Califano JA, Clary B, Cohen EEW, Kane C, et al. Positive surgical margins in the 10 most common solid cancers. Sci Rep. 2018;8:5686.
8. Luryi AL, Chen MM, Mehra S, Roman SA, Sosa JA, Judson BL. Positive surgical margins in early stage oral cavity cancer: an analysis of 20, 602 cases. Otolaryngol Head Neck Surg. 2014;151:984–90.
9. Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. Oral Oncol. 2007;43:780–4.
10. Chen TY, Emrich LJ, Driscoll DL. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. Int J Radiat Oncol Biol Phys. 1987;13:833–7.
11. Jacobs JT, Ahmad K, Casiano R, Schuller DE, Scott C, Laramore GE, et al. Implications of positive surgical margins. Laryngoscope. 1993;103:64–8.
12. Jones AS. Prognosis in mouth cancer: tumor factors. Eur J Cancer B Oral Oncol. 1994; **30B**;30:8–15.
13. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg. 2003;32:30–4.
14. Genden E, Ferlito A, Silver CE, et al. Contemporary management of cancer of the oral cavity. Eur Arch Otorhinolaryngol. 2010;267:1001–17.
15. Curran AJ, Toner M, Quinn A, et al. Mandibular invasion diagnosed by SPECT. Clin Otolaryngol Allied Sci. 1996;21:542–5.
16. Mukherji SK, Isaacs DL, Creager A, Shockley W, Weissler M, Armao D. Ct detection of mandibular invasion by squamous cell carcinoma of the oral cavity. AJR Am J Roentgenol. 2001;177:237–43.
17. Li C, Men Y, Yang W, Pan J, Sun J, Li L. Computed tomography for the diagnosis of mandibular invasion caused by head and neck cancer: a systematic review comparing contrast-enhanced and plain computed tomography. J Oral Maxillo Fac Surg. 2014;72(8):1601–15.
18. Li C, Yang W, Men Y, Wu F, Pan J, Li L. Magnetic resonance imaging for diagnosis of mandibular involvement from head and neck cancers: a systematic review and meta-analysis. PLoS One. 2014;9(11):e112267.
19. Arya S, Rane P, Sable N, Juvekar S, Bal M, Chaukar D. Retromolar trigone squamous cell cancers: a reappraisal of 16 section MDCT for assessing mandibular invasion. Clin Radiol. 2013;68:e680–8.
20. Nemzek WR, Hecht S, Gandour-Edwards R, Donald P, McKennan K. Perineural spread of head and neck tumors: how accurate is MR imaging? AJNR Am J Neuroradiol. 1998;19:701–6.
21. Ong CK, Chong VF. Imaging of perineural spread in head and neck tumors. Cancer Imaging. 2010;10(Spec no A):S92–8.
22. Le G. Perineural tumor spread associated with head and neck malignancies. In: Som PM, Curtin HD, editors. Head and neck imaging. 5th ed. St. Louis: Elsevier Mosby; 2011. p. 1021–39.
23. Imaizumi A, Yoshino N, Yamada I, Nagumo K, Amagasa T, Omura K, et al. A potential pitfall of MR imaging for assessing mandibular invasion of squamous cell carcinoma in the oral cavity. AJNR Am J Neuroradiol. 2006;27:114–22.
24. Lam P, Au Yeung KM, Cheng PW, et al. Correlating MRI and histologic tumor thickness in the assessment of oral tongue cancer. AJR Am J Roentgenol. 2004;182:803–8.
25. Arya S, Rane P, Deshmukh A. Oral cavity squamous cell carcinoma: role of pretreatment imaging and its influence on management. Clin Radiol. 2014;69:916–30.
26. Johnson RE, Signman JD, Funk GF. Quantification of surgical margin shrinkage in the oral cavity. Head Neck. 1997;19:281–6.
27. Mistry RC, Qureshi SS, Kumaran C. Post-resection mucosal margin shrinkage in oral cancer: quantification and significance. J Surg Oncol. 2005;91:131–3.
28. Priya SR, D'Cruz AK, Pai PS. Cut margins and disease control in oral cancers. J Cancer Res Ther. 2012;8:74–9.
29. McMahon JD, Devine JC, Hetherington J, Bryson G, McLellan D, MacIver C, et al. Involved surgical margins in oral and oropharyngeal carcinoma-an anatomical problem? Br J Oral Maxillofac Surg. 2011;49:172–5.
30. Iseli TA, Lin MJ, Tsui A, Guiney A, Wiesenfeld D, Iseli CE. Are wider surgical margins needed for early oral tongue cancer? J Laryngol Otol. 2012;126:289–94.
31. Nason RW, Sako K, Beecroft WA, Razack MS, Bakamjian VY, Shedd DP. Surgical Management of Squamous cell carcinoma of the floor of mouth. Am J Surg. 1989;158:292–6.
32. Ota Y, Aoki T, Karakida K, Otsuru M, Kurabayashi H, Sasaki M, et al. Determination of deep surgical margin based on anatomical

architecture for local control of squamous cell carcinoma of the buccal mucosa. Oral Oncol. 2009;45:605–9.

33. Liao CT, Huang SF, Chen IH, Chang JT, Wang HM, Ng SH, et al. When does skin excision allow the achievement of an adequate local control rate in patients with squamous cell carcinoma involving the buccal mucosa? Ann Surg Oncol. 2008;15:2187–94.
34. Mahmood S, Conway DI, Ramesar K. Use of intra-operative cytological assessment of mandibular marrow scrapings to predict resection margin status in patients with squamous cell carcinoma. J Oral Maxillofac Surg. 2001;59:1138–41.
35. Oxford LE, Ducic Y. Intraoperative evaluation of cortical bony margins with frozen-section analysis. Otolaryngol Head Neck Surg. 2006;134:138–41.
36. Wysluch A, Stricker I, Holzle F, Wolff K-D, Maurer P. Intraoperative evaluation of bony margins with frozen-section analysis and trephine drill extraction technique: a preliminary study. Head Neck. 2010;32:1473–8.
37. Weisberger EC, Hilburn M, Johnson B, Nguyen C. Intraoperative microwave processing of bone margins during resection of head and neck cancer. Arch Otolaryngol Head Neck Surg. 2001;127: 790–3.
38. NCCN Principles of surgery - Magin SURG-A page 3 of 9 v1.2015, National Comprehensive Cancer Network Inc. Head and Neck Cancer.
39. Williams MD. Determining adequate margins in head and neck cancers: practice and continued challenges. Curr Oncol Rep. 2016;18:54.
40.• Tarabichi O, Kanumuri V, Juliano AF, Faquin WC, et al. Intraoperative ultrasound in oral tongue cancer resection: Feasibility Study and Early Outcomes. Otolaryngol Head Neck Surg. 2018;58(4): 645–8. **A preliminary report on the use of ultrasound to confirm clearance of the deep margin as an adjunct to palpation for oral tongue cancers.**
41. Baek CH, Seon YI, Jeong HS, et al. Intraoral sonography assisted resection of T1-2 tongue cancer for adequate deep resection. Otolaryngol head Neck Surg. 2008;139:805–10.
42. Kodama M, Khanal A, Habu M, Iwanaga K, Yoshioka I, Tanaka T, et al. Ultrasonography for intraoperative determination of tumor thickness and resection margin in tongue carcinomas. J Oral Maxillofac Surg. 2010;68:1746–52.
43. Cantazaro S, Copelli C, Manfuso A, Tewfik K, Pederneschi N, Cocchi CLR. Intraoperative navigation in complex head and neck resections: indications and limits. Int J CARS. 2017;12:881–7.
44. Bitterman G, Scheifele C, Prokic V, Chatt V, Henke M, Grosu AL, et al. Description of a method: computer generated virtual model for accurate localization of tumor margins, standardized resection, and planning of radiation treatment in head and neck cancer surgery. J Craniomaxillofac Surg. 2013;41(4):279–81.
45. Ma AK, Daly M, Quin J, Chan HHL, Goldstein DP, Irish JC, et al. Intraoperative image guidance in transoral robotic surgery: a pilot study. Head Neck. 2017;39(10):1976–83.
46. King E, Daly MJ, Chan H, Bachar G, Dixon BJ, Siewerdsen JH, et al. Intraoperative cone-beam CT for head and neck surgery: feasibility of clinical implementation using a prototype mobile C-arm. Head Neck. 2013;35(7):959–67.
47. Yang SW, Lee YS, Chang LC, Hwang CC, Chen TA. Diagnostic significance of narrow-band imaging for detecting high-grade dysplasia, carcinoma in situ, and carcinoma in oral leukoplakia. Laryngoscope. 2012;122(12):2754–61.
48. Tirelli G, Piovesana M, Gatto A, Tofanelli M, Biasotto M, Boscolo Nata F. Narrow band imaging in the intra-operative definition of resection margins in oral cavity and oropharyngeal cancer. Oral Oncol. 2015;51(10):908–13.
49. Rosenthal EL, Warram JM, de Boer E, Chung TK, Korb ML, Brandwein-Gensler M, et al. Safety and tumor specificity of cetuximab-IRDye800 for surgical navigation in head and neck cancer. Clin Cancer Res. 2015;21:3658–66.
50.•• Rosenthal EL, Moore LS, Tipirneni K, de Boer E, Stevens TM, Hartman YE, Carroll WR, Zinn KR, Warram JM. Sensitivity and specificity of cetuximab-IRDye800CW to identify regional metastatic disease in head and neck cancer. Clin Cancer Res. 2017;23: 4744–52. **This group's efforts in developing a cancer-targeting agent to more specifically identify cancer cells intra-operatively is cumulated into this study whereby the cancer-targeting agent was able to localize regional metastatic disease.**
51. James ML, Gambhir SS. A molecular imaging primer: modalities, imaging agents, and applications. Physiol Rev. 2012;92:897–965.
52. Koch M, Ntziachristos V. Advancing surgical vision with fluorescence imaging. Annu Rev Med. 2016;67:153–64.
53. Harmsen S, Teraphongphom N, Tweedle MF, Basilion JP, Rosenthal EL. Optical surgical navigation for precision in tumor resections. Mol Imaging Biol. 2017;19:357–62.
54. Barth CW, Gibbs SL. Direct administration of nerve-specific contrast to improve nerve sparing radical prostatectomy. Thernostics. 2017;7:573–93.
55. KleinJan GH, Buckle T, van Willigen DM, Oosterom M, Spa S, Kloosterboer H, et al. Fluorescent lectins for local in vivo visualization of peripheral nerves. Molecules. 2014;19:9876–92.
56. Kang S, Wang Y, Reder NP, Liu JT. Multiplexed molecular imaging of biomarker-targeted SERS nanoparticles on fresh tissue specimens with channel-compressed spectrometry. PLoS One. 2016;11:e163473.
57. Harmsen S, Huang R, Wall MA, Karabeber H, Samii JM, Spaliviero M, et al. Surface-enhanced resonance Raman scattering nanostars for high-precision cancer imaging. Sci Transl Med. 2015;7(271):271ra7.
58.•• Aubreville M, Knipfer C, Oetter N, Jaremenko C, et al. Automatic classification of cancerous tissue in Laser endomicroscopy images of the oral cavity using deep learning. Sci Rep. 2017;7:11979. **A novel method using artificial intelligence and deep learning for the accurate and automated detection of confocal laser endomicroscopy images of oral cavity squamous cell cancer.**
59. Garvey PB, Chang EI, Selber JC, et al. A prospective study of preoperative computer tomographic angiographic mapping of free fibula osteocutaneous flaps for head and neck reconstruction. Plast Reconst Surg. 2012;130:541e–50e.
60.• Rommel N, Kesting MR, Rohleder NH, et al. Mandible reconstruction with free fibula flaps: outcome of a cost-effective individual planning concept compared with virtual surgical planning. J Craniomaxillofac Surg. 2017;45:1246–50. **This group describes a cost-effective, and simple planning concept with stereolithographic models for free fibula mandibular reconstruction with similar operative time and post-operative outcomes to virtual surgical planning.**
61. Hanasono MM, Skoracki RJ. Computer-assisted design and rapid prototype modeling in microvascular mandible reconstruction. Laryngoscope. 2013;123:597–604.
62. Gangopadhyay N, Villa MT, Chang EI, Selber JC, Liu J, Garvey PB. Combining preoperative CTA mapping of the peroneal artery and its perforators with virtual planning for free fibular flap reconstruction of mandibulectomy defects. Plast Reconstr Surg. 2015;136(Suppl):8–9.
63. Largo RD, Garvey PB. Updates in head and neck reconstruction. Plast Reconstr Surg. 2018;141:271e–85e.
64.•• Chang EI, Jenkins MP, Patel SA, Topham NS. Long-term operative outcomes of preoperative computer tomography-guided virtual surgical planning for osteocutaneous free flap mandible reconstruction. Plast Reconstr Surg. 2016;137:619–23. **This is one of the largest and longest single institution retrospective reviews comparing virtual surgical planning against prefabricated stereolithic models in fibular free flap reconstruction of**

mandibular defects and found significant decreased operative time, and fewer rates of bony nonunion with virtual surgical planning.

65. Ramella V, Franchi A, Bottoso S, et al. Triple cut computer-aided design-computer-aided modeling: more oncologic safety added to precise mandible modeling. J Oral Maxillofac Surg. 2017;75: 1567e1–6.
66. Nakao M, Aso S, Imai Y, Ueda N, Hatanaka T, Shiba M, et al. Automated planning with multivariate shape descriptors for fibular transfer in mandibular reconstruction. IEEE Trans Biomed Eng. 2017;64:1772–85.
67. Riediger D. Restoration of masticatory function by microsurgically revascularized iliac crest bone grafts using endosseous implants. Plast Reconstr Surg. 1988;81:861–77.
68. Sozzi D, Novelli G, Silva R, Connelly ST, Tartaglia GM. Implant rehabilitation in fibula-free flap reconstruction: a retrospective study of cases at 1-18 years following surgery. J Craniomaxillofac Surg. 2017;45:1655–61.
69. Barber AJ, Butterworth CJ, Rogers SN. Systematic review of primary osseointegrated dental implants in head and neck oncology. Br J Oral Maxillofac Surg. 2011;49:29–36.
70. Ch'ng S, Skoracki RJ, Selber JC, et al. Osseointegrated implant-based dental rehabilitation in head and neck reconstruction patients. Head Neck. 2016;38(Suppl):E321–7.
71. Barber BR, Dziegelewski PT, Chuka R, et al. Bone-impacted fibular free flap: long-term dental implant success and complications compared to traditional fibular free tissue transfer. Head Neck. 2016;28:E1783–7.
72. Dziegielewski PT, Mlynarek AM, Harris JR, Hrdlicka A, Barber B, al-Qahtani K, et al. Bone impacted fibular free flap: a novel technique to increase bone density for dental implantation in osseous reconstruction. Head Neck. 2014;36:1648–53.
73. Levine JP, Bae JS, Soares M, Brecht LE, Saadeh PB, Ceradini DJ, et al. Jaw in a day: Total maxillofacial reconstruction using digital technology. Plast Reconstr Surg. 2013;131:1386–91.