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Current Role of Surgery in the Management of Oropharyngeal Cancer

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Abstract

The 1990s saw an increased use of chemoradiotherapy protocols, commonly referred to as organ-sparing therapy, for the treatment of oropharyngeal cancer after the Groupe d'Oncologie Radiothérapie Tête Cou trial. Since that time, human papillomavirus–associated oropharyngeal squamous cell carcinoma has been identified as a unique disease, with improved survival regardless of treatment modality. The improved outcomes of this population has led to re-evaluation of treatment paradigms in the past decade, with a desire to spare young, human papillomavirus–positive patients the treatment-related toxicities of chemoradiotherapy and to use new minimally invasive surgical techniques to improve outcomes. Numerous retrospective and prospective studies have investigated the role of surgery in treatment of oropharyngeal carcinoma and have demonstrated equivalent oncologic outcomes and improved functional outcomes compared with chemoradiotherapy protocols. Ongoing and future clinical trials may help delineate the role of surgery in the future.

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INTRODUCTION

Historically, surgical treatment of oropharyngeal squamous cell carcinoma (OPSCC) beyond select, early tonsillar primaries required large, invasive, open approaches to create exposure for en bloc extirpation with negative margins. Open approaches include mandibular lingual release,[1] transpharyngeal approaches (lateral or suprahyoid pharyngotomies),[2,3] and transmandibular approaches (midline labiomandibuloglossotomy or composite resection with segmental mandibulectomy).[4] Because of the functional morbidity and complications associated with open approaches, organ-sparing concurrent chemoradiotherapy protocols became the standard of care after the GORTEC (Groupe d'Oncologie Radiothérapie Tetê et Cou) trial and others.[5–7]

Today, there are two distinct types of patients with OPSCC: the older, human papillomavirus(HPV)–negative patient, who has a large primary cancer and history of tobacco and alcohol abuse along with a high risk of second primary cancers from field cancerization[8]; and the younger, HPV-positive patient, who is a nonsmoker and nondrinker[9] with a small, sometimes undetectable primary, large cervical nodes, and dramatically improved overall survival.[6] The identification of HPV-positive OPSCC has challenged treatment paradigms, because patients are surviving to suffer the long-term toxicities from organ-sparing therapy.

The discovery of HPV-positive OPSCC and recent development of minimally invasive transoral surgical techniques have renewed interests in surgical management of OPSCC. Transoral laser microsurgery and transoral robotic surgery are oncologically sound surgical treatments without the morbidity of open approaches. In this review, we provide evidence supporting surgical treatment of OPSCC.

OROPHARYNGEAL CANCER: EPIDEMIOLOGY

The decreasing smoking incidence in the United States has led to a decreased incidence of aerodigestive squamous cell carcinoma, except for OPSCC, in a recent SEER-based study.[10] According to the Centers for Disease Control and Prevention, there are 11,726 new cases of OPSCC diagnosed each year in the United States. Since 2003, HPV is known to be the causal agent in both retrospective and prospective studies.[11,12] Between 1988 and 2004, there has been a 225% population-level increase in HPV-positive OPSCC and a 50% decline in HPV-negative OPSCC.[12] Today, an estimated 70% of OPSCC cases are HPV positive, and this epidemic has been documented in populations around the world (Canada, the United Kingdom, Australia, Denmark, and Slovakia).[13]

ORGAN-SPARING PROTOCOLS: FUNCTIONAL OUTCOMES

Pooled data from RTOG 91-11, RTOG 97-03, and RTOG 99-14 trials show that 35% of OPSCC survivors have severe late toxicity (chronic grade 3 or 4 pharyngeal toxicity, gastrostomy dependence beyond 2 years, and/or treatment-related death within 3 years).[14] A recent study suggests that late-onset dysphagia affects 60% of survivors treated with concurrent chemoradiotherapy, which was higher compared with groups treated by surgery, radiation, or both.[15] The true incidence of severe late-onset dysphagia is not known, but it is

known to be treatment refractory and devastating to survivors' quality of life. Because the HPV-positive patient with OPSCC has improved survival after initial response, regardless of progression of disease,[16] minimally invasive transoral surgery may improve care and prevent treatment-related toxicity in this group.

TRANSORAL LASER MICROSURGERY: BACKGROUND

Steiner first began using endoscopic transoral laser microsurgery as treatment of tumors of the upper aerodigestive tract in the 1980s. The technique was originally popularized for the treatment of laryngeal and hypopharyngeal carcinomas. Since then, it has been used to treat advanced-stage OPSCC with control rates comparable to surgical and nonsurgical treatments.[17–20]

Technical advantages of transoral laser microsurgery include microscopic visualization of the tumor interface, maximum preservation of normal tissue, and intraoperative tactile feedback.[17] Although early tonsillar carcinomas are easily removed en bloc, removal of large or base-of-tongue carcinomas often cannot be performed without division of the specimen.[18] Therefore, opponents of this technique site piecemeal removal and the risk of positive margins as major disadvantages. Despite reported successes in large retrospective studies, transoral laser microsurgery for OPSCC is only practiced in a few high-volume centers.[17–20]

TRANSORAL LASER MICROSURGERY: SURGICAL PROCEDURE

The procedure begins with exposure of the tumor using the laryngoscope. An operating microscope then illuminates and magnifies the field. Ideally, all margins can be visualized with a single view. In the base of the tongue, multiple repositioning maneuvers may be necessary to visualize all margins.[18] Excision proceeds in segmental fashion, or segmentally, using the CO_2 laser. The surgeon inks the true margins intraoperatively and sends them for frozen section analysis. Resection continues until negative margins are achieved. Neck dissections are then performed in a single session.

TRANSORAL LASER MICROSURGERY FOR OROPHARYNGEAL CANCER

Several retrospective, single-institution studies report comparable oncologic outcomes for the treatment of OPSCC with transoral laser microsurgery. Canis et al[17] reported oncologic and functional outcomes in a series of 102 patients treated by transoral laser microsurgery for OPSCC of the tonsil in a study conducted between 1986 and 2007. Locoregional control rates for early and advanced tumors were 75% and 78%, respectively. Five-year overall, recurrence-free, and disease-free survival were reported as 59%, 64%, and 74%, respectively, for T1 and T2 tumors. For T3 and T4 tumors, they were 56%, 60%, and 68%, respectively. Only 3% of patients remained gastrostomy dependent. The same group conducted a similar study in 82 patients treated with this approach for OPSCC of the tongue base.[18] The local control rate was 84% for all patients. Local recurrence rates for T1/T2, T3, and T4 tumors were 94%, 78%, and 81%, respectively. For all patients, 5-year overall

survival was 59%, and recurrence-free survival was 69%. The gastronomy dependence rate was 6% because of recurrent aspiration.

In a nonrandomized, prospective, multicenter trial of 204 patients with advanced oropharyngeal cancer, Haughey et al[19] examined 3-year overall survival, disease-specific survival, and disease-free survival, which were 86%, 88%, and 82%, respectively, comparable to previous series using concurrent chemoradiotherapy. The group also examined functional outcomes using the Functional Outcome Swallowing Scale and gastrostomy dependence as end points. Scores were significantly worse for patients undergoing adjuvant radiotherapy and adjuvant chemoradiotherapy compared with those undergoing transoral laser microsurgery alone. Only 3.4% were gastrostomy dependent at 3-year follow-up, with 87% of patients reporting normal or episodic dysphagia.

TRANSORAL ROBOTIC SURGERY: BACKGROUND

In 2000, the Food and Drug Administration approved the da Vinci robot (Sunnyvale, CA) for use in general surgery. Applications in head and neck surgery were then explored as early as 2003, in a porcine model of robotic neck surgery.[21] Hockstein et al[22] at the University of Pennsylvania pioneered the use of transoral robotic surgery in the oropharynx in human cadaveric models in 2006. This was quickly followed by the first human trial containing 62 patients who underwent robotic surgery as the sole treatment of OPSCC of the tonsil, glossotonsillar sulcus, and/or base of tongue.[23] Food and Drug Administration approval for robotic surgery in the head and neck was granted in 2009, and, subsequently, multiple clinical trials have been proposed.

Transoral robotic surgery for the treatment of OPSCC has gained popularity, because this technique uses angled endoscope instruments for improved visualization and exposure over traditional techniques, as well as articulating robotic arms for easier and more precise dissection of the parapharyngeal and submandibular spaces. The superiority of robotic approaches compared with others is most obvious in the base of the tongue, where it provides binocular, three-dimensional, high-definition exposure and access from the circumvallate papilla to the vallecula.[24] Critics of robotic surgery cite the costliness of the da Vinci system and increased operative times as disadvantages. Since then, studies looking at cost-effectiveness have been performed, finding robotic approaches superior.[25]

TRANSORAL ROBOTIC SURGERY: SURGICAL PROCEDURE

The patient is intubated and the tumor exposed with mouth gag retractors. The robot is then docked near the patient’s head, and the working arms, cautery, and forceps are inserted transorally. The surgeon then sits at the remote console with binocular, high-definition, three-dimensional microscopy and tremor-free hand controls. At the head, the assistant provides counter-traction, suction, and hemostasis as needed. Elective or therapeutic neck dissections may be performed concurrently, before, or after transoral robotic surgery, depending on indications for transoral robotic surgery and/or surgeon preference.[26] For example, base-of-tongue resection being performed for the unknown primary may require a staged neck dissection, because the primary tumor may not be identified until final

pathologic analysis. Some argue that concurrent neck dissection allows for ligation of the external carotid artery branches (lingual, facial, and ascending pharyngeal), which significantly decreases the severity of postoperative bleeding.[27]

TRANSORAL ROBOTIC SURGERY FOR OROPHARYNGEAL CANCER

Oncologic outcomes after robotic surgery for OPSCC have been reported in small series (Table 1). In 2012, Weinstein et al[23] reported on outcomes after primary robotic surgery without the use of adjuvant therapy for oropharyngeal cancer in 30 patients and reported 100% overall survival and 97% locoregional control at 2 years. The largest multicenter study of 410 patients demonstrated 91.8% 2-year locoregional control and 94.5% disease-specific survival, with only half of patients requiring adjuvant radiotherapy (31.3%) or chemoradiotherapy (21.3%).[29] A systematic review comparing 12 studies using transoral robotic approaches versus eight studies using intensity-modulated radiotherapy for early OPSCC was published in 2014.[31] Oncologic outcomes were similar at 2 years. A similar meta-analysis performed by Morisod and Simon[32] concluded that 5-year overall survival and disease-specific survival were equivalent to nonsurgical treatments. Overall, the results after robotic surgery compare favorably with intensity-modulated radiotherapy outcomes for early T-stage OPSCC in the literature.[33]

Functional outcomes after robotic surgery for OPSCC have also been reported in retrospective series. A recent systematic review looking at 12 papers reporting functional outcomes in 441 patients found that gastrostomy dependence rates were lower than those reported for intensity-modulated radiation.[34] When looking at a subset of 89 patients with reported MD Anderson Dysphagia Indices, patients undergoing robotic surgery had better scores (65.2–78) compared to those undergoing nonsurgical therapy (73.6–74.1).

TRANSORAL SURGERY FOR CANCER OF THE UNKNOWN PRIMARY

According to Motz et al,[35] the incidence of cancer of unknown primary origin is increasing, with the majority being HPV related. Byrd et al[25] localized 19 of 22 patients (86.4%) with nonlocalizing physical examinations and imaging using robotic surgery, similar to other groups.[36,37] This number drops to 67% when patients have negative physical examinations, imaging, and directed biopsies. Lingual tonsillectomy identified the primary in 72% (18 of 25) of cases. The major benefit of surgery in this setting is identification of the primary, which prevents wide-field irradiation of the entire aerodigestive tract, pharyngeal constrictors, and neck required when the primary cannot be pathologically determined. A recent, retrospective case-control study by Davis et al[38] found that HPV status is associated with improved overall survival in patients with unknown primary cancers and that identification of the primary tumor is associated with significantly improved overall, cause-specific, and disease-free survival.

SURGICAL SALVAGE FOR OROPHARYNGEAL CANCER

Despite improved prognosis, 25% of patients with HPV-positive OPSCC will experience recurrence after primary therapy.[6,16] Still, patients with recurrent HPV-positive tumors have

improved overall survival compared with HPV-negative patients.[16,39] Salvage transoral robotic surgery has been performed with an acceptable complication rate without routine reconstruction.[16,40] Furthermore, patients undergoing surgical salvage or recurrent OPSCC have improved survival compared with those undergoing nonsurgical salvage.[39] Recently, Fakhry et al[16] looked at a retrospective cohort of 86 patients with recurrence OPSCC who received salvage therapy. HPV status, surgical salvage, and response to salvage were predictors of overall survival. Margin status at time of salvage was the only predictor of disease-free survival.[16]

SURGERY AS PREVENTION

Recently, groups have looked into whether prior tonsillectomy has an impact on the incidence of OPSCC. Studies looking at the Swedish and Danish cancer registries found that tonsillectomy significantly reduced the risk of developing tonsillar carcinoma.[41,42] A more recent study looking at the North Carolina Central Cancer Registry examined the effect of prior tonsillectomy on the incidence of oropharyngealc arcinomaby subsite.[43] This group found that tonsillectomy was associated with a two-fold increase in the risk of base-of-tongue carcinoma (odds ratio, 1.95; 95% CI, 1.25 to 3.06; $P = .003$), particularly when tonsillectomy was performed at a young age. These studies highlight the theoretical role of prophylactic surgery in prevention of OPSCC. However, the risk to individuals and the cost to society cannot be justified without identification of a high-risk patient or premalignant changes. For that reason, the current literature does not warrant prophylactic surgery for OPSCC.

ONGOING CLINICAL TRIALS

The toxicities of chemoradiotherapy are well known to medical and radiation oncologists, who are exploring treatment deintensification via altered fractionation, decreased radiation doses, less-toxic chemotherapy, and immunotherapy regimens for HPV-positive OPSCC. Similarly, trials are underway to improve surgical treatment of OPSCC and de-escalation of adjuvant treatment.[44,45]

Extracapsular spread is considered an adverse feature, conferring poor prognosis in patients with head and neck cancer, and is therefore an indication for adjuvant chemoradiotherapy when found in neck dissection specimens. The incidence of extracapsular spread in surgically treated OPSCC has been studied using the National Cancer and SEER databases and is estimated at 23% to 25%, increasing with higher N stages.[46,47] Recent retrospective studies by Sinha et al[48] and Maxwell et al[46] demonstrate that this feature does not negatively affect survival in HPV-positive OPSCC and may not require adjuvant chemoradiotherapy for successful treatment of this population. In 2013, the ADEPT (Adjuvant Deescalation, Extracapsular Spread, p16 Positive, Transoral) trial was launched to determine the benefit of chemotherapy in patients with HPV-positive OPSCC with extracapsular spread, using 2-year locoregional control and disease-free survival as end points. Until these results come in, some surgically treated patients with OPSCC will receive trimodality treatment, because extracapsular extension cannot be predicted by preoperative imaging and will be diagnosed in surgical specimens.[49]

The ECOG 3311 trial is a national phase II randomized, prospective trial examining transoral surgery for resectable, lateralized stage III or IV, HPV-positive OPSCC (cT1-T2, N1-2b) without matted nodes, followed by adjuvant therapy as guided by risk assessment. Low-risk patients (T1–T2, N0 or N1 with negative margins) are observed. Intermediate-risk patients (close margins, two to four positive lymph nodes, extracapsular spread ≤ 1 mm, lymphovascular/perineural invasion) are randomly assigned to 50 Gy versus 60 Gy adjuvant radiation. High-risk patients (positive margins, more than five positive lymph nodes, > 1-mm extracapsular spread) receive adjuvant chemoradiotherapy with 66 Gy and cisplatin. More than 50 centers are credentialed and participating in the trial.[15] An estimated 500-patient enrollment will be needed to determine significance of deintensification in the intermediate group, using 2-year progression-free survival as an end point. To date, approximately 55% have been placed in the intermediate-risk arm and 12% in the low-risk arm, with 39% receiving deintensified therapy.[45] Of note, the trial passed its data safety monitoring committee review without cessation for excess toxicity or futility. Patient-reported outcomes on quality of life and swallowing analysis are being collected.

Currently, the ORATOR (Oropharynx: Radiotherapy Versus Trans-Oral Robotic Surgery) trial, a phase II trial of HPV-positive and -negative OPSCC comparing transoral robotic surgery–based treatment to radiation with or without chemotherapy, is underway. It is a single-institution prospective trial in London, Ontario, with a required enrollment of 68 patients and a primary end point of quality-of-life outcomes at 1 year.[44] Secondary end points include overall survival and progression-free survival. Although well conceived, this study would require more patients and a minimum follow-up of 2 years to make more definitive, meaningful conclusions.

DISCUSSION

The major argument favoring the use of transoral surgery (laser or robotic) in the treatment of oropharyngeal carcinoma is to spare the young, HPV-positive patient with stage III or IV disease the debilitating side effects of concurrent chemoradiotherapy. Reports of swallowing function (< 2 years) after transoral laser surgery and robotic surgery are not well studied; however, several studies report low rates of dysphagia and gastrostomy dependence (0% to 7%) beyond the first year postsurgery.[29,34,50]

Outside of a clinical trial, many patients with OPSCC routinely receive chemoradiotherapy after transoral surgery, which is one of the major arguments against primary surgical management.[31] High rates of adjuvant chemoradiotherapy are attributable to the elevated incidence of nodal metastases and extracapsular spread in HPV-positive pathologic specimens.[46,47] Extracapsular spread was originally identified as a poor prognostic indicator in two randomized controlled trials of advanced head and neck cancer that have made it an indication for adjuvant chemoradiotherapy under the current standard of care.[51] However, these studies were flawed because they grouped all head and neck subsites together, the majority of patients had OPSCC, and results were not stratified by HPV status. In a study examining surgically treated early oropharyngeal cancer with both open and transoral techniques, Kass et al[30] reported that recurrence-free survival was 82% and that HPV status and the use of adjuvant radiotherapy was protective against recurrence, whereas nodal status

and the addition of chemotherapy had no impact. A group looking at the National Cancer Database found that positive margins and extracapsular spread did not affect survival in surgically treated HPV-positive patients with OPSCC.[52] In the future, extracapsular spread may not be an indication for adjuvant chemoradiotherapy; however, level 1 evidence will be required to change current practice.

Several factors should be considered when selecting patients with OPSCC for surgery (ie, patient preference and overall health). Careful work-up including physical examination, imaging, endoscopy, and swallowing evaluation may influence surgical candidacy. Patients need evidence-based counseling regarding risks and benefits of the different treatment modalities after discussion in a multidisciplinary tumor board. Relative contraindications to surgery in our practice are obvious extracapsular spread on imaging, significant palatal involvement, vallecula involvement requiring supraglottic resection, and T_4 tumors.

In summary, transoral surgery for OPSCC achieves similar outcomes compared with organ-sparing techniques and should be considered in HPV-positive patients. Surgery for treatment of cancer of the unknown primary may lead to identification of the primary, improved survival, and better quality of life. Open transpharyngeal and transmandibular approaches should be reserved for surgical salvage; however, salvage transoral surgery may have a role and provide superior functional and oncologic outcomes in select patients. Prophylactic surgery is not warranted as prevention. Prospective, randomized trials are under way to define the role of transoral surgery. Future trials will ideally compare surgical versus nonsurgical approaches in the HPV era.

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Table 1

Surgery for the Treatment of Oropharyngeal Squamous Cell Carcinoma

First Author	Design	Treatment	Subsites	Tumor	N	LC	LRC	OS	DFS	RFS	Adjuvant	G-tube (%)	Year
Canis[18]	Single-center retrospective study	TLM	Base of tongue (100%)	T1–T4	82	84% overall	NS NS NS	70% (stage I–II) 44% (stage III) 58% (stage IV)	NS NS NS	86% (stage I–II) 54% (stage III) 69% (stage IV)	NS NS NS	6% overall	2013
Canis[17]	Single-center retrospective study	TLM	Tonsil (100%)	T1–T4 (T3/T4, 84%)	102	NS	78% (T1–T2) 75% (T3–T4)	59% (stage I–II) 56% (stage III–IV)	74% (stage I–II) 68% (stage III–IV)	64% (stage I–II) 60% (stage III-IV)	66% with RT	4% overall	2013
Grant[28]	Two-center retrospective review	TLM	Base of tongue (42%) Tonsil (41 %) Pharyngeal wall (12%) Soft palate (6%)	T1–T3	69	94% overall	90% (stage I) 73% (stage II) 70% (stage III)	NS	NS	NS	76% with RT	0% overall	2009
Weinstein[23]	Single-center, prospective study	TORS	Tonsil (47%) Base of tongue (30%) Glossotonsillar sulcus (10%) Palate (10%)	T1–T4	30	97% at 2 years	97% at 2 years	100% at 2 years	NS	NS	No adjuvant RT No adjuvant chemotherapy	0% overall	2012
Haughey[19]	Multicenter prospective study	TLM	Tonsil/palate (48%) Base of tongue (52%)	T1–T4	204	97% overall	87.3% overall	78% overall	74% overall	NS	58% with RT 16% with CRT	3.8% (5-year)	2011
de Almeida[29]	Multicenter retrospective review	TORS	Oropharynx (88%) Tonsil (45.4%) Base of tongue (31.7%) Faucial arch/pharyngeal wall (8%) Soft palate (3.4%)	Tx–T4(≤T2,86.2%)	364	95.60%	88.8% (3-year) Tonsil (2.7%) Base of tongue (6.2%) Faucial arch/pharyngeal wall (17.6) Soft palate (14.3%)	87.1% (3-year)	NS	NS	39.0% no adjuvant 31.3% with RT 21.3% with chemotherapy 17.6% unknown	NS	2015
Kass[30]	Two-center study	Any method 42% TORS 45% TLM/ transoral 13% open	NS *	T1–T2	143	NS	NS	NS	NS	82% (regardless of surgical approach) 87% (TORS)	16.1% overall 40% (stage III, N+) 0% with CRT	NS	2016

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; G-tube, gastrostomy tube; LC, local control; LRC, locoregional control; NS, not specified; OS, overall survival; RFS, recurrence-free survival; RT, radiotherapy; TLM, transoral laser microsurgery; TORS, transoral robotic surgery.

*Early 5 T1/T2N0, intermediate 5 T1/T2N1.