Transoral Endoscopic Head and Neck Surgery and Its Role Within the Multidisciplinary Treatment Paradigm of Oropharynx Cancer: Robotics, Lasers, and Clinical Trials

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ABSTRACT

Transoral endoscopic head and neck surgery is a new approach for the treatment of oropharyngeal tumors. Using either a robotic system and/or laser, surgeons gain access through the mouth via minimally invasive technique and thus have improved visualization of the tumors of the oropharynx, without disfiguring incisions. This transoral route of access minimizes long-term speech and swallowing dysfunction. Surgeons view this approach as a considerable technologic advance, analogous to the evolution in radiation therapy from conventional two- and three-dimensional conformal techniques to intensity-modulated techniques. Although the use of radiation with or without chemotherapy to treat oropharyngeal cancer (OPC) is supported by evidence from prospective clinical trials, there are no prospective data supporting the use of this new surgical approach for OPC. Here, we review the fundamentals of transoral endoscopic head and neck surgery, with robotics and laser technology, and discuss ongoing clinical trials for patients with OPC.

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INTRODUCTION

Oral and pharyngeal carcinoma represents a significant public health problem worldwide, with more than 400,000 new cases per year, ranging from seven to 17 cases per 100,000 persons,¹ and affecting nearly 46,000 individuals this year alone in the United States.² Chaturvedi et al³ have recently described the striking association between oropharyngeal cancer (OPC), human papillomavirus (HPV), and the startling new epidemiology of this disease. From 1988 to 2004, HPV-positive OPC increased by 225% (95% CI, 208% to 242%; from 0.8 per 100,000 to 2.6 per 100,000), whereas the incidence of HPV-negative cancers declined by 50% (95% CI, 47% to 53%; from 2.0 per 100,000 to 1.0 per 100,000). Patients with HPV-associated OPC tend to be nonsmokers, male, and younger than traditional patients with head and neck cancer.⁴ Does this evolving epidemiology of OPC change the role of surgery within the multidisciplinary treatment paradigm? As we will discuss, the role of new techniques in transoral endoscopic head and neck surgery varies based on the varying clinical needs of HPV-positive and HPV-negative patients with OPC.

In the past, most surgery for OPC was performed through transfacial, transmandibular in-

cisions,⁵ yet many patients still required extensive adjuvant therapy postoperatively. Poor function and concern for cosmesis led multidisciplinary teams to explore alternative options, such as concurrent chemotherapy with radiation therapy (ccRT).^{6,7} Although effective in terms of locoregional control, ccRT can be associated with significant delayed toxicity, as well as adverse functional effects. Dysphagia remains perhaps the most important functional impairment in survivors of OPC.⁸ Late grade 3 to 4 laryngopharyngeal toxicity more than 5 years after treatment was reported in 35% of 101 survivors of OPC who had adequate baseline function in a pooled analysis of three Radiation Therapy Oncology Group (RTOG) trials of concomitant chemoradiotherapy,⁹ and the 3-year prevalence of dysphagia approaches 50% based on population-level data from survivors of OPC in the Surveillance, Epidemiology, and End Results–Medicare database.¹⁰ With the recent publication of the first prospective data demonstrating the value of intensity-modulated radiation therapy (IMRT) for head and neck cancer,¹¹ it is hoped that late effects beyond the acute and subacute treatment window will also be reduced, although data here are lacking. Therefore, despite the advantages of nonsurgical organ preservation offered by ccRT,

Fig 1. Transoral robotic head and neck surgery is performed by a surgeon sitting at a remote console (back left of photograph) manipulating a binocular endoscope and two additional instruments that are placed in the mouth. Real surgery is performed using a virtual environment, affording the surgeon with enhanced visualization of the target surgical anatomy and minimizing the morbidity of the surgical approach by operating through the mouth. The surgeon controls every move made by the robotic system, which is programmed with a master-slave configuration.

concerns about long-term toxicity and swallowing function have driven the pursuit of new approaches.¹²

TRANSORAL ENDOSCOPIC HEAD AND NECK SURGERY

Transoral endoscopic head and neck surgery (eHNS)¹³ has emerged as a vital part of multidisciplinary care for head and neck cancer, especially for OPC. Transoral eHNS is minimally invasive transoral oncologic surgery of the oropharynx performed with either carbon dioxide laser microsurgery (transoral laser microsurgery [TLM])¹⁴ and/or robotic surgery (transoral robotic surgery [TORS]).¹⁵ These new surgical approaches may provide improved functional outcomes with minimal surgical morbidity or enhance surgical and pathologic staging to selectively intensify high-risk patients for improved survival.

Compared with classic transcervical or open head and neck surgery, eHNS is performed without external incisions and obviates the need for mandibulotomy or transmandibular access. Transoral eHNS is surgery from the inside out because incisions begin from the mucosal (inner) surface and extend outward, eliminating any skin incisions. Using a microscope and a carbon dioxide laser for TLM or the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) for TORS, a comprehensive oncologic resection of the primary tumor is performed through the mouth. Although both TLM and TORS rely on a minimally invasive approach through this transoral route, there are a few differences between these two eHNS techniques.

TLM

TLM is performed under direct laryngoscopy, with suspension/fixation and the use of an operating microscope, microsurgical instruments, and a carbon dioxide laser. It is an adaptive surgical technique, relying on the surgeon's understanding of the three-dimensional anatomy of the tumor's extent and surrounding anatomy. First described in 1972,¹⁶ TLM has a robust literature. Steiner¹⁷ first described dividing the tumor as a means to understand the full depth and extent of the lesion, then circumferentially and rationally resecting surrounding

adjacent soft tissues. Skeptics have criticized this approach because it diverts from the classic principles of Halstead, whereas advocates cite the potential for a more precise resection of surrounding tissues. Although a single multicenter experience has been published,¹⁸ no prospective coordinated clinical trial has been performed.

TORS

In 2009, the US Food and Drug Administration approved the use of the da Vinci Surgical System for transoral otolaryngology.¹⁹ Transoral robotic head and neck surgery is performed by a surgeon sitting at a remote console manipulating an endoscopic and two additional instruments that are placed in the mouth. Real surgery is performed using a virtual environment, affording the surgeon enhanced visualization of the target surgical anatomy and minimizing the morbidity of the surgical approach by operating through the mouth. The surgeon controls every move made by the robotic system, which is programmed with a master-slave configuration (Fig 1). A suitable oral retractor is positioned in the mouth, and the endoscope or camera is introduced into the pharynx followed by the two other arms carrying interchangeable 5- or 8-mm-wide working instruments (eg, grasping forceps and electrocautery; Fig 2). The surgeon is provided with an endoscopically derived three-dimensional visual display that is collocated with control handles that direct movements of the robot's instruments inside the patient's body. Standard surgical instruments, including tissue forceps, a spatulated electrocautery device, or carbon dioxide²⁰ and thulium laser,²¹ are then used to perform an en bloc resection of the oropharyngeal tumor. A bedside assistant provides countertraction and suction while caring for the patient throughout the procedure (Fig 3).

Indications for TORS

Indications and contraindications for TORS relate to both patient factors and tumor characteristics. Patients must have transoral access to the oropharynx. In a study of 51 adult human cadavers, Arora et al²² found that mandibular body height, hyoid-mental length, and

Fig 2. Close-up view: an oral retractor is placed in the mouth and opened to provide exposure. A binocular endoscope and two other instruments, such as grasping forceps and electrocautery spatula, are introduced, permitting the surgeon to perform the surgery remotely through a console with three-dimensional visualization of deep oropharyngeal anatomy.

neck circumference, in addition to the degree of mouth opening, may determine patient suitability for TORS. Retrognathia, class II dental occlusion, limited cervical extension, and prominent maxillary dentition may create difficulty in gaining comprehensive access to the oral cavity and pharynx and may be relative contraindications.

T1-2 tumors of the oropharynx are usually amenable to resection but only when the surgeon has good oral access. Tumors arising within the tonsillar fossa and lateral pharyngeal wall, glossopharyngeal sulcus, and lateral tongue base are particularly well suited to resection via TORS. Tumors within this area have predictable lymphatic drainage and offer a good chance for functional recovery. Other tumors may be accessible transorally but may pose other limitations. For instance, the use of transoral endoscopic approaches for tumors of the soft palate may result in a higher rate of rhinolalia and velopharyngeal insufficiency and nasopharyngeal reflux.²³ Tumors of the posterior oropharyngeal walls are quite accessible, but a first echelon of nodal drainage to the retropharyngeal nodes²⁴ and bilateral drainage for these midline tumors complicate decision making for adjuvant surgical lymphadenectomy.

Because the surgical wounds after TORS heal by secondary intention, the health of epithelial mucosa and potential for recovery are paramount. Therefore, patients with previous radiation therapy or connective tissue or rheumatologic disease should be advised to expect longer healer time. Delayed mucosal healing may correlate with postoperative complications, especially bleeding. Likewise, patients who require antithrombotic therapy or anticoagulation are also not ideally suited to TORS because these wounds are open and may have edges susceptible to hemorrhage.

Since the first report on robotic surgery for an oropharyngeal tumor was published in 2005,²⁵ a rich retrospective literature has emerged supporting the role of TORS for T1-2 OPC. In these largely single-institution studies, the rates of disease control for T1-2 disease

have been comparable to those seen with ccRT. Weinstein et al²⁶ reported 100% locoregional control for T1-3 tonsillar carcinoma in 27 patients. Reporting for the Mayo group, Moore et al²⁷ reported 3-year local and regional disease control rates of 97.0% and 94.0%, respectively, for 66 patients. Two-year disease-specific and recurrence-free survival rates were 95.1% and 92.4%, respectively. Recently, the largest experience of head and neck TORS was presented, demonstrating a 2-year locoregional control rate of 91.8% and overall survival rate of 91.0% in 410 patients treated in 11 centers across the world.²⁸ In this multicenter experience, 90% of patients undergoing TORS had primary tumors arising in the oropharynx, suggesting that the primary role of TORS is this anatomic subset of the head and neck anatomy. Eighty-four percent of patients who underwent TORS had T1-2 tumors, again suggesting the optimal tumor stage for this surgical modality. Patients with tonsillar tumors had better locoregional control compared with patients with tumors of the faucial arch, and oncologic outcomes seemed to be independent of association with HPV.

In contrast to treatment with ccRT, oncologic outcomes after primary treatment with TORS may be independent of HPV status. In RTOG 0129, Ang et al⁷ highlighted the significant impact HPV status had on the treatment of 720 patients with T2-4N1-3 OPC. Patients with HPV-positive tumors had an overall survival rate of 82.4% compared with 57.1% for HPV-negative patients ($P < .001$). For patients undergoing TORS, there seems to be no clear link between HPV status and benefit from surgical resection. Whether by polymerase chain reaction²⁹ or p16 immunohistochemistry,³⁰ smaller studies suggest no prognostic impact of HPV status for T1-2 patients with resectable OPC when treated with an initial TORS approach. In addition, adverse pathologic risk factors, such as N2b status, presence of extracapsular extension (ECE), or a close/positive margin, do not seem to confer as significant a prognostic impact in HPV-positive OPC.

Fig 3. A bedside assistant provides countertraction and suction and cares for the patient throughout the procedure.

Thus, up-front surgery may provide insight into the potential differences in the use of TORS in HPV-positive and HPV-negative patients and its potential in the management of recurrence. However, skeptics of TORS remain wary of this approach, citing concerns about surgical margins and the high rate of radiation therapy required postoperatively,³¹ ranging from 60% of patients³² to 90%.²⁶ Lukens et al³³ reporting from the University of Pennsylvania have also highlighted the potential risks of triple-modality therapy. Despite these concerns, two studies have shown high rates of locoregional control for patients treated with TORS only as up-front therapy. Weinstein et al³⁴ reported 97% local control with minimum follow-up and 90% regional control for 30 selected TORS patients not receiving any postoperative adjuvant therapy. This cohort represented 7% of the overall TORS experience at the University of Pennsylvania. For 34 patients treated with TORS alone at the University of Pittsburgh, only two patients (6%) experienced disease recurrence without any additional therapy, and the whole cohort demonstrated significant improvement in three global quality-of-life (QOL) scales over the 24 months after surgery.³⁵

Functional Outcomes

Functional outcomes in speech and swallowing decline rapidly in the immediate postoperative period after TORS but return back to

baseline within 2 to 3 weeks of surgery, before adjuvant therapy might need to be administered. The University of Alabama at Birmingham showed that most patients undergoing TORS are discharged home with an oral diet (69%) or within 2 weeks (83%).³⁶ The need for a longer term feeding gastrostomy tube was associated with both higher T stage (T3-4 v T1-2) and patients with recurrent tumors after previous radiation therapy. Dziegielewski et al³⁷ presented detailed patient-reported outcomes for 81 patients undergoing TORS. Although overall declines were seen initially in speech, eating, aesthetic, social, and overall QOL domains early on in the postoperative period after TORS, by 1 year after surgery, patient-reported QOL scores returned to a high level of patient satisfaction using the Head and Neck Cancer Inventory and the health-related QOL instruments.

In contrast, Machtay et al⁹ demonstrated a risk of progressive and sometimes severe, long-term toxicities of nearly 50% in patients receiving ccRT, even on RTOG-sponsored clinical trials. Thus, front-line transoral eHNS may lead to improvements in functional outcomes and QOL compared with other front-line treatments.

TORS may also be selectively used for patients with recurrent disease after primary radiation therapy with or without chemotherapy. White et al³⁸ compared the role of TORS versus standard open surgery in TNM stage-matched patients who underwent surgical salvage treatment. Patients treated with TORS were found to have a significantly lower incidence of tracheostomy use ($P < .001$) and feeding tube use ($P < .001$) and shorter overall hospital stays. The 2-year recurrence-free survival rate was significantly higher in the TORS group than in the open approach group (74% and 43%, respectively; $P = .01$). Although TORS may play a role in this population, wound healing and functional recovery are significantly delayed compared with patients undergoing TORS without previous radiation therapy.

Both transoral eHNS techniques (TLM and/or TORS) provide a highly magnified view of the tumor, which allows confident resection of various tumor invaginations that are not often visualized with standard surgical techniques. Compared with open surgery, eHNS is minimally invasive. Numerous publications demonstrate a reduction in immediate postoperative toxicity, shorter postoperative hospitalization time, and faster functional recovery compared with open surgery.^{15,27,39} Advocates for eHNS (TLM and/or TORS) in oncologic surgery cite excellent functional results and argue that eHNS may reduce the long-term toxicity that is sometimes associated with a primary radiation-based approach for OPC.^{15,39,40}

PROSPECTIVE CLINICAL TRIALS IN TRANSORAL EHNS

The use of ccRT to treat OPC is supported by a preponderance of data generated from prospective clinical trials funded both by industry and the National Cancer Institute (NCI). However, for transoral eHNS, there are no prospective data supporting its primary use for the treatment of OPC. Whereas numerous retrospective single-institution reports and a few important multicenter trials have generated significant enthusiasm for implementing eHNS into the multidisciplinary approach, prospective clinical evidence to support its use is limited.

In 2011, Adelstein and Ridge organized an NCI-sponsored, R13-funded Clinical Trials Planning Meeting⁴¹ to integrate transoral eHNS

into the multidisciplinary treatment paradigm of OPC. A multidisciplinary team of more than 50 oncologists and experts in speech therapy, statistics, and economics came to the consensus that further investigation of transoral surgery for OPC was an important priority for the head and neck oncology cooperative groups in North America.

Two phase II trials were designed to explore the potential of eHNS, Eastern Cooperative Oncology Group (ECOG) 3311 and RTOG 1221, which both opened in the Fall of 2013. ECOG 3311 examines the role of transoral eHNS to reduce toxicity in patients with intermediate-risk stage III/IV HPV-associated (p16-positive) OPC, whereas RTOG 1221 explores the role of surgery to intensify locoregional therapy with up-front surgery in poorer prognosis high-risk p16-negative OPC. For p16-positive OPC, the ECOG 3311 trial would study deintensification of postoperative adjuvant therapy. For HPV-negative OPC, RTOG 1221 would study the ability of transoral eHNS to improve oncologic outcomes through surgical intensification. Common eligibility criteria for transoral eHNS were standardized across both protocols. Only patients with tumors of the oropharynx staged as T1-2, N1-2b, M0 are eligible. Primary tumors must be localized to Waldeyer's ring—the palatine tonsil, glossopharyngeal sulcus, and lateralized tongue base. In addition to common eligibility criteria, surgeon credentialing and quality assurance were established.

CREDENTIALING

One novel aspect of the two NCI-sponsored surgical trials is the establishment of shared credentialing criteria and ongoing quality assurance for transoral endoscopic head and neck surgeons. To participate, surgeons must document significant experience and clinical volume in their practice. Each surgeon must attest to have performed transoral resection of T1-2 OPC, using either TORS or TLM. Furthermore, surgeons must document that 10 of these transoral resections were performed within the past 24 months. Finally, surgeons must be working at institutions and hospitals with an affiliation with these cooperative groups, such as the NRG (formerly the RTOG), the ECOG/American College of Radiology Imaging Network, and/or the Community Clinical Oncology Program. Once they meet these criteria, individual surgeons and their clinical research team must submit the following documentation: paired reports including surgical pathology and operative notes for 10 patients with OPC performed within the last 2 years from the time of submission. The histology of resected tumors from these submitted patient cases should primarily be squamous cell carcinoma, although a minority could come from salivary or other rare malignant histology.

However, all patient cases must demonstrate tumor within the specimen and adequate margin assessment in the pathology report. Either HPV-positive or HPV-negative squamous cell carcinoma is acceptable, provided that it is from an oropharyngeal site, preferably tongue base or tonsil. Unknown primary cancers are acceptable provided that a primary tumor was found and margins were assessed systematically.

Credentialing is granted based on each type of transoral eHNS modality, either TORS or TLM. Thus, surgeons requesting credentials for TLM must submit documentation for surgery of 10 OPCs performed by TLM. Likewise, 10 OPC surgeries performed by

TORS must be presented to request credentials for TORS. It is possible and encouraged for surgeons capable in both techniques to credential in both TLM and TORS. However, this would require 20 total OPC cases (10 TLM; 10 TORS) to be submitted. In other words, credentialing and approval for E3311 and RTOG 1221 is technology specific.

Functional assessment of outcomes for these trials will be an important secondary outcome. Therefore, in addition to surgeon credentialing, speech and swallowing rehabilitation teams must also submit documentation ensuring standardized technique and quality assessment for video fluorographic swallowing studies or modified barium swallow studies to be performed.

A panel of transoral endoscopic head and neck surgeons and ECOG and RTOG cooperative group surgical leadership was assembled to review and approve surgeon credentials. These nine experienced surgeons meet monthly by teleconference to review new or revised case submissions and to establish criteria for approval, on-hold status, and ongoing quality assurance. This process was successfully implemented in 2013 and led to approval of 62 credentialed surgeons with accrual capability.

Finally, specimen handling and margin assessment by pathology have been standardized across these two NCI-funded clinical trials. Common reporting templates will facilitate careful microscopic analysis of surgical margins and quantitated measurement (ECE) of lymph node metastasis. This was adapted from the College of American Pathologists guideline for OPC pathology reporting.

ECOG E3311

A major objective of ECOG E3311 (Fig 4) is to establish the feasibility of a prospective multi-institutional study of transoral eHNS (TLM and TORS) followed by risk-adjusted adjuvant therapy for patients with p16-positive OPC. The primary objective is to demonstrate that up-front surgery can permit reduced dose (deintensified adjuvant therapy), comparing 50 Gy versus 60 Gy in a randomized trial. The primary end point is to assess the oncologic efficacy (to achieve 85% 2-year disease-free survival) of a novel treatment approach for patients with intermediate-risk stage III/IV surgically resected cancers based on pathologic staging. These intermediate-risk pathologic features include close margins (< 3 mm), the presence of two to four metastatic lymph nodes, or ECE of tumor outside any of these nodes of less than 1 mm. These intermediate-risk patients are randomly assigned to receive either a standard postoperative dose of 60 or a study dose of 50 Gy. For patients randomly assigned to 60 Gy, the ipsilateral nodal regions involved with carcinoma and the primary surgical site will receive a 10-Gy boost to a total of 60 Gy. The 2-year progression-free survival rate will be used to evaluate the efficacy in the intermediate-risk group. An estimated 377 patients are required assuming 226 patients (60%) with intermediate-risk pathologic features. As of April 2015, E3311 has demonstrated safety and feasibility in the 135 patients accrued, in terms of grade 3 or 4 bleeding rate, positive margins, and surgical quality. Thus far, patients have been distributed into the different postoperative arms in keeping with estimated proportions, as follows: 11% in arm A (observation), 58% in arms B versus C of randomly assigned radiotherapy dose, and 31% in arm D for cisplatin chemoradiotherapy in patients with high-risk pathologic features (ie,

Fig 4. The schema for the ongoing Eastern Cooperative Oncology Group (ECOG) 3311 clinical trial studying the role of transoral endoscopic head and neck surgery for patients with p16-positive oropharyngeal carcinoma. Total estimated accrual is 377 patients. CDDP, cisplatin; ECS, extracapsular spread; Fx, fractions; H&N, head and neck; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; LN, lymph node; LVI, lymphovascular invasion; PFS, progression-free survival; PNI, perineural invasion; QOL, quality of life; SCC, squamous cell carcinoma.

extensive [> 1 mm] ECE or positive margins). Grade 3 bleeding has been acceptable at a rate of 3%. Sixty-two surgeons from 50 centers in North America are credentialed for accrual on this trial.

RTOG 1221

RTOG 1221 was designed for patients with p16-negative OPC and first opened for enrollment in October 2013. A total of 29 surgeons were credentialed across 26 centers. Unfortunately, after 15 months, no patients had been accrued to the study. An informal survey of investigators found a surprising paucity of eligible p16-negative patients with stage T1-2, N1-2b disease within the tonsil, tongue base, or glossopharyngeal sulcus. Surgeons reported that most HPV-negative tumors were presenting with more advanced

tumor classification and were not suitable for transoral eHNS. The NRG Oncology Head and Neck Cancer Surgical Committee found a decline in the observed number of these eligible T1-2, p16-negative tumors compared with what was predicted in 2011 at the Clinical Trials Planning Meeting based on trends identified in RTOG 0129.⁷ An additional concern was the feasibility of mounting two prospective surgical trials across the clinical research enterprise in head and neck surgery programs. Concern was also raised on the part of a few physicians and patients for whom random assignment of up-front therapy might have been difficult to implement, given embedded treatment preferences and perceived lack of control over therapeutic decision making. These were the primary reasons for the NCI's decision to close this trial in February 2015.

Table 1. Ongoing Clinical Trials Evaluating the Role of Transoral Endoscopic Head and Neck Surgery

Trial	Phase	Inclusion Criteria	Treatment Arms	No. of Patients	Outcome	Status
ADEPT, NCT01687413	III	T1-4a, N+ OPC, p16-positive s/p TORS with ECE	IMRT 60 Gy $\pm$ weekly cisplatin	496	2-year DFS/LRC	Recruiting
PATHOS, NCT02215265	II/III	T1-3, N0-2b, p16-positive OPC, < 10 pack-year smoking history	IMRT 50 v 60 Gy (intermediate risk) or 60 Gy $\pm$ cisplatin (high risk)	242	2-year PFS	Recruiting
ORATOR, NCT01590355	II	T1-2, N0-1 (≤ 3 cm) or N2b (up to 2 nodes ≤ 3 cm) OPC	TORS + neck dissection v IMRT $\pm$ chemotherapy	68	1-year QOL	Recruiting
E3311, NCT01898494	II	Stage III, IVA/B OPC, p16 positive	TORS $\rightarrow$ low risk = observation; intermediate risk = IMRT 50 Gy v 60 Gy; high risk = 66 Gy + cisplatin	377	2-year DFS	Recruiting
EORTC 1420-HNCG-ROG	III	Stage I/II, OPC HPV positive and negative	TLM/TORS + neck dissection v IMRT	160	1-year QOL	Opens Q1 2016

Abbreviations: ADEPT, Adjuvant De-escalation, Extracapsular Spread, p16-Positive, Transoral; DFS, disease-free survival; ECE, extracapsular extension; EORTC, European Organisation for Research and Treatment of Cancer; HNCG-ROG, Head and Neck Cancer Group–Radiation Oncology Group; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; LRC, locoregional control; OPC, oropharyngeal cancer; ORATOR, Oropharynx: Radiotherapy Versus Trans-Oral Robotic Surgery; PATHOS, Post-Operative Adjuvant Treatment for HPV-Positive Tumours; PFS, progression-free survival; Q1, first quarter; QOL, quality of life; s/p, status post; TLM, transoral laser microsurgery; TORS, transoral robotic surgery.

OTHER ONGOING CLINICAL TRIALS

In addition to these NCI-funded clinical trials, several other efforts are under way in the United States and worldwide to study transoral eHNS (Table 1). The Adjuvant De-escalation, Extracapsular Spread, p16-Positive, Transoral (ADEPT) Trial for oropharynx malignancy was launched in 2013 by Haughey and colleagues at Washington University, Mayo Clinic Scottsdale, and the University of Texas Southwestern Medical Center in Dallas. In this trial, a shared decision-making treatment model is used for the selecting postoperative adjuvant therapy. Patients could choose postoperative radiation or concurrent radiation based on pathology findings or be randomly assigned. A total of 496 patients will be accrued to this study and accrual is under way. The schema and rationale for the ORATOR trial was previously published before accrual.⁴² The ORATOR trial will compare functional outcomes of patients with early-stage OPC treated with radiotherapy versus TORS.

Parallel clinical trials are launching in Europe to study transoral eHNS. PATHOS (Post-Operative Adjuvant Treatment for HPV-Positive Tumours) is a phase II/III trial to examine the impact of transoral eHNS on swallowing function for patients with HPV-associated OPC and the impact of less intensive adjuvant treatment on locoregional disease control and survival. EORTC (European Organisation for Research and Treatment of Cancer) 1420 is a multi-center prospective phase III trial led by a collaboration of the EORTC, the French Groupe Oncologie Radiothérapie Tête et Cou (GORTEC), and other European head and neck surgical cooperative groups. Scheduled to open in late 2015 or early 2016, this study will also examine functional and oncologic outcomes of patients treated with transoral eHNS and postoperative adjuvant IMRT or primary radiation therapy for both HPV-positive and -negative T1-2N0 OPC (C. Simon, personal communication, June 2015). The primary objective of the study is to assess and compare postoperative swallowing function within the first year for patients treated in the two arms. Patient-reported outcomes assessed by The University of Texas MD Anderson

Dysphagia Index⁴³ will be used at 12 and 24 months to discern differences between the two treatment arms. In this phase III randomized trial, patients will be randomly assigned 1:1 after eligibility is confirmed and results will be stratified by the following variables: institution performing transoral eHNS, HPV status, smoking status, T stage, and oropharyngeal subsite.

In summary, transoral eHNS represents a considerable technological advance in surgical technique, akin to the difference between conventional two- and three-dimensional conformal radiotherapy versus IMRT. As such, transoral eHNS has been included in the most recent National Comprehensive Cancer Network guidelines for patients with OPC.⁴⁴ Despite this evolving consensus about the role of minimally invasive approaches to treat OPC, this surgical approach, including the impact of margins and the role of postoperative radiation therapy after TORS and TLM, must be carefully studied. Ongoing clinical trials worldwide and the newly established surgical credentialing process in the United States should provide light on the role of this new approach for patients with head and neck cancer and, in particular, tumors of the oropharynx.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

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Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Transoral Endoscopic Head and Neck Surgery and Its Role Within the Multidisciplinary Treatment Paradigm of Oropharynx Cancer: Robotics, Lasers, and Clinical Trials

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