

Current Indications for Transoral Robotic Surgery in **Oropharyngeal Cancer**

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KEYWORDS

- Oropharyngeal cancer
 Transoral robotic surgery
 Throat cancer
- Human papillomavirus

KEY POINTS

- The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing dramatically and is conclusively linked to increasing rates of human papillomavirus (HPV) infection.
- HPV-related oropharyngeal cancers have been shown to occur in a unique demographic group and show favorable oncologic outcomes compared with HPV-negative OPSCC.
- There has been a paradigm shift in the treatment of early-stage OPSCC, with most patients now undergoing primary surgery in the United States.
- Transoral robotic surgery is associated with excellent oncologic and functional outcomes in the treatment of OPSCC and is increasingly being used for a broader range of oropharyngeal indications.

Video content accompanies this article at http://www.oto.theclinics.com.

INTRODUCTION

This article discusses the changing epidemiology of oropharyngeal squamous cell carcinoma (OPSCC), which has become a key factor in the development of robotics in otolaryngology. It discusses the evolution of the treatment paradigm of OPSCC, from historical open procedures, to advances in radiotherapy and chemoradiation, to the contemporary development of novel transoral procedures, including robotic surgery. In so doing, it describes the shift in patient demographics and outcomes in the human papilloma virus era of OPSCC and how this has affected the landscape of therapy. A detailed review of the current oncologic indications for transoral robotic

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Otolaryngol Clin N Am 53 (2020) 949-964 https://doi.org/10.1016/j.otc.2020.07.007 0030-6665/20/© 2020 Elsevier Inc. All rights reserved. surgery (TORS) is presented as well as a description of the most common surgical procedures: radical tonsillectomy and base of tongue resection.

EPIDEMIOLOGY

Head and neck cancer represents the sixth most common cancer worldwide, with more than 700,000 new cases in 2018.¹ Among them, there has been a notable increase in the incidence of OPSCC, with an estimated annual incidence of 92,887 worldwide.¹ In contrast, the rates of cancer in other subsites of the head and neck have decreased, likely because of lower rates of smoking and alcohol use over the past several decades.^{2,3} The increasing incidence of OPSCC has been most pronounced in North America, northern Europe, and Australia.^{4–11}

The dramatic increase has been shown, through epidemiologic, molecular, and case-control studies, to be conclusively linked to human papillomavirus (HPV) coinfection.^{12–15} In the United States alone, the incidence of HPV-mediated OPSCC increased by 225% between 1998 and 2004.¹² The proportion of OPSCC related to HPV infection varies around the world, with HPV implicated in up to 80% of US cases of OPSCC, but fewer than 20% of OPSCCs in countries with higher rates of tobacco use.¹⁶ The variable global distribution has led some to propose that changes in sexual behaviors (eg, oral sex, multiple sexual partners) among contemporary cohorts have led to increased oral HPV exposure and associated cancer risk.^{4,9,12,16–19} The increased incidence of OPSCC is associated not only with certain geographic locations but also with a unique demographic cohort: young (between 40 and 55 years of age) white men, often without a strong history of alcohol or tobacco use.^{10,16}

Another distinct feature of HPV-mediated OPSCC is its tendency to originate in the lingual and palatine tonsil subsites, because the virus is thought to preferentially target the reticulated epithelium lining the tonsillar crypts.^{20,21} Importantly, HPV-associated OPSCC is associated with a more favorable prognosis compared with HPV-negative OPSCC.^{21,22} This prognosis is thought to be related not only to higher response rates to therapy but also to the absence of field cancerization from tobacco and alcohol. HPV-positive patients are also more likely to have excellent performance status and fewer comorbidities.^{16,23–25}

HISTORICAL PERSPECTIVE ON OROPHARYNGEAL CANCER TREATMENT

Waldeyer's²⁶ nineteenth century microscopic studies were the first to show that squamous cancers in the head and neck originated from epithelial surfaces. One early well-documented case occurred in 1884 when America's 18th President, Ulysses S. Grant, developed a right tonsillar carcinoma.^{27,28} He underwent a sub-total resection and topical cocaine therapy, which provided some degree of palli-ation but did not arrest tumor growth, eventually eroding through his palate.²⁷ He had a sentinel bleed in the spring of 1885 and passed away shortly thereafter.^{27,28}

Advances in aseptic technique, general anesthesia, and airway management allowed nineteenth century innovation in head and neck surgery. In 1846 at Harvard, John Warren was the first to remove a cervical tumor under general anesthesia.^{29,30} In 1862, Theodore Billroth³¹ described the transmandibular approach to the oral cavity and oropharynx.^{31,32} Subsequently, in 1880, Theodor Kocher³³ described transcervical techniques to obtain arterial control of head and neck tumors.^{29,30,33}

Despite advances, head and neck surgery was associated with prohibitive morbidity, and the treatment of head and neck cancer in the early to mid-

twentieth century was therefore dominated by radiotherapy, a new and promising entity.^{29,32} However, failure rates of single-modality radiotherapy (up to 95%) and the complications associated with salvage surgery prompted a revival of surgical efforts.^{29,32} In the 1940s and 1950s, New York surgeon Hayes Martin popularized the so-called commando operation, which involved a lip split, segmental mandibulectomy, and in-continuity neck dissection for oral cavity and oropharyngeal malignancy.²⁹ Despite subsequent refinements, such as mandibular lingual release and transpharyngeal approaches, radical approaches continued to dominate the oropharyngeal landscape despite high levels of morbidity and stagnating cure rates.^{34–36} Between the 1970s and 1990s, radiotherapy again gained prominence, initially as an adjunct, and later as primary therapy alongside new chemotherapeutics (eg, chemoradiotherapy [CRT]).³⁷ Eventually, CRT became routinely used as primary therapy for because it was thought to offer similar oncologic results with preservation of form and function.^{38,39} However, CRT came with its own set of morbidities, including mucositis and dysphagia, and many patients later required salvage procedures.40,41

CURRENT TECHNIQUES IN OROPHARYNGEAL SURGERY

In the late twentieth and early twenty-first century, the dramatic increase in OPSCC incidence driven by HPV oncogenicity became an impetus for innovation in minimally invasive techniques. Although radical tonsillectomy had been described as early as 1951 by Huet⁴² and the technique had been practiced by head and neck surgeons throughout the late twentieth century, there were no published studies assessing clinical outcomes in these patients. In the early twenty-first century, Laccourreye and colleagues⁴³ and Holsinger and colleagues⁴⁴ developed a standardized technique for radical tonsillectomy using cold knife and electrocautery. However, these techniques were limited by a lack of adequate visualization of the tongue base and limited access to reliably obtain negative margins. Haughey and colleagues⁴⁵ and other investigators described transoral laser microsurgery (TLM) as an alternative surgical technique that provides improved visualization and hemostasis with excellent oncologic outcomes; however, this technique did not become widely adopted.

The limitations of existing techniques for transoral access to the oropharynx prompted the development of a novel application of robotics. Initially used in general surgery, obstetrics and gynecology, and urology, the da Vinci Surgical System (Intuitive Surgical Inc, Sunnyvale, CA) was pioneered for use in transoral surgery at the University of Pennsylvania. In 2005, initial studies on human cadavers and canines confirmed the feasibility of its application.^{46,47} Excellent visualization, decreased line of sight issues (using a 30° endoscope), and the addition of an assistant at the head of the bed allowed modification of the Huet procedure to perform a reliable radical tonsillectomy without the limitations associated with the original technique.⁴⁸ A standardized radical base of tongue resection technique was subsequently developed.⁴⁹ With these 2 standardized TORS procedures, most early-stage oropharyngeal tumors could be reliably treated with primary surgery.

Additional robotic systems, including the Medrobotic Flex system (Medrobotics, Raynham, MA) and accompanying oropharyngeal retractors, have since been pioneered and tested successfully.^{50,51} The da Vinci robot now hosts the Si (US Food and Drug Administration [FDA] approved), Xi (off-label), and new SP (off-label, single port) systems.⁵²

OROPHARYNGEAL INDICATIONS FOR TRANSORAL ROBOTIC SURGERY Early-Stage Oropharyngeal Cancers

Outcomes from successful multi-institutional retrospective trials led to the FDA approval of TORS for benign and T1/T2 malignant otolaryngologic tumors in 2009.⁵³ Although TORS has been used to manage numerous disorders, it is most commonly used for resection of early-stage OPSCC. American population-based data have shown that the percentage of patients undergoing primary surgery for T1/T2 OPSCC increased from 56% in 2004 to 82% in 2013. This shift has been driven by patient preference, excellent oncologic results, encouraging functional results, and advances in surgical robotic technology.^{54,55} To better understand which patients with OPSCC are best suited to an upfront surgical approach, it is important to consider contraindications.

Contraindications to TORS can be categorized as vascular, functional, oncologic, and nononcologic.⁵⁶ Vascular contraindications include tonsillar cancer with a retropharyngeal carotid artery, tumor in the midline tongue base putting both lingual arteries at risk, tumor adjacent to carotid bulb or internal carotid artery, and tumor or metastatic node encasing carotid artery.^{56,57} Functional contraindications include tumor resection requiring more than 50% of the deep tongue base musculature, the posterior pharyngeal wall, the tongue base, or the entire epiglottis.⁵⁶ Oncologic contraindications include unresectable tumor (involving lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, prevertebral fascia), unresectable neck disease, neoplastic-related trismus, and multifocal distant metastases.⁵⁶ Additional nononcologic contraindications include systemic disease associated with unacceptable morbidity in the perioperative period, non–cancer-related trismus preventing robotic access, and cervical spine disease interfering with patient positioning and neck extension.⁵⁶

Many investigators advocate that patients with T1/T2 OPSCC who are able to minimize or avoid postoperative adjuvant therapy are best suited to an upfront TORS approach. Upfront TORS has the potential to reduce and/or eliminate the need for adjuvant therapy in certain cases, and numerous encouraging treatment deescalation trials are currently underway. A full discussion of treatment deescalation can be found in a separate Benjamin Wahle and Jose Zevallos' article, "Transoral Robotic Surgery and De-escalation of Cancer Treatment," in this series.

Oncologic results for early-stage OPSCC treated with upfront TORS have been very favorable (Table 1). Early studies published by Weinstein and colleagues⁴⁸ showed a 100% locoregional control rate for selected T1 to T3 tonsillar cancers (N = 27), as well as a 93% 2-year disease-specific survival rate in a subsequent study including all oropharyngeal subsites (N = 50, T1–T4).⁵⁸ Moore and colleagues⁵⁹ showed 3-year local and regional disease control rates of 97% and 94%, respectively, as well as 2-year disease-free and recurrence-free survival rates of 95% and 92%, respectively (N = 66; 84.9% T1/T2). A recent large multicenter study of 410 patients undergoing TORS (89% OPSCC) showed 2-year disease-specific and overall survival rates of 95% and 91% respectively.⁶⁰ Of these patients, 84% were T1/T2, 70% were HPV positive (of those with known status), and 47% underwent surgery alone without need for adjuvant therapy. This finding was also consistent with a recent systematic review of 772 patients that showed 2-year survival estimates of 82% to 94% for early-stage OPSCC treated with upfront TORS.⁶¹

Functional outcomes following TORS are also encouraging (Table 2). In a study of 38 patients with OPSCC treated with upfront TORS (86.9% T1/T2), Leonhardt and colleagues⁶² showed that although decreases in diet-related indices were observed early

Table 1 Oncologic outcomes following transoral robotic surgery for oropharyngeal squamous cell carcinoma																
Study	N	T Stage	p16+ (%)	Negative Margins (%)	Adjuvant Therapy (%)			Overall Survival (%)			Disease-Specific Survival (%)			Recurrence-Free Survival (%)		
					S Alone (%)	S + XRT (%)	S + CRT (%)	1-у	2-у	5-y	1-у	2-у	5-у	1-y	2-у	5-у
Weinstein et al, ⁴⁸ 2007	27	T1–T3	_	92.6	7.4	33.3	55.6	No su	No survival data provided — — — –						_	
Cohen et al, ⁵⁸ 2011	50	T1–T4a	74.0	94.0	18.0	24.0	54.0	95.7	80.6	_	97.8	92.6	_	_	_	
Moore et al, ⁵⁹ 2012	66	T1–T4a	66.7	98.0	16.7	21.2	62.0	_	_	_	_	95.1	_	_	92.4	
De Almeida et al, ⁶⁰ 2015	410	T1–T4a	69.4	69.1	47.3	31.4	21.3	_	91.0	_	_	94.5	_	_	_	
Sharma et al, ⁹⁹ 2016	39	T1–T3	97.0	_	10.3	61.5	28.2	Survi	val com	nparabl	le to m	atched	contro	ols (CR1	Γ)	
Moore et al, ¹⁰⁰ 2018	314	T1–T4a	93.0	98.0	24.0	28.0	48.0	98.0	_	86.0	99.0	_	94.0	98.0	_	98.0
Dhanireddy et al, ¹⁰¹ 2019	65	T1–T2	80.0	_	25.0	37.5	37.5	_	82.3	70.2	_	_	_	_	_	_
Total	971	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_

Abbreviations: S, surgery; XRT, radiotherapy. Data from Refs.^{48,58–60,99–101}

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				Trache	ostomy	Gastrost	omy Tube	HRQOL (Overall QOL)			
Study	N	T Stage	Tumor Site	Temporary (%)	Permanent (%)	Temporary (%)	Permanent (%)	Baseline	6 mo	12 mo	
Weinstein et al, ⁴⁸ 2007	27	T1–T3	Tonsil	_			3.7	_	_	_	
Moore et al, ⁵⁹ 2012	66	T1–T4a	Tonsil, BOT	25.8	1.5	27.2	4.5	_	_	_	
Dziegielewski et al, ¹⁰² 2013	81	T1–T4a	Tonsil, BOT, SP	1	0	21	11	76.3 (21.7)	66.0 (25.8)	76.8 (20.5)	
Kelly et al, ⁶³ 2014	190	T1–T2	_	_	0	_	5	_	_		
Sharma et al, ⁹⁹ 2016	39	T-T3	Tonsil, BOT	_		9	3	_	_	_	
Achim et al, ¹⁰³ 2018	74	T1–T2	Tonsil, BOT	1.4	0	9	1	_	_	_	
Sethia et al, ¹⁰⁴ 2018	111	T1–T4a	Tonsil, BOT	0	0	44.1	10.8	_	_	_	
Van Abel et al, ¹⁰⁵ 2019	267	T1–T4	_	11	0.7	28.8	2.2	_	_		

QOL reported as mean (standard deviation).

Permanent is defined as more than 12 months postoperative. Abbreviations: BOT, base of tongue; HRQOL, health-related quality of life; QOL, quality of life; SP, soft palate. Data from Refs.^{48,59,63,99,102–105}

after TORS, all patients returned to baseline quality of life and functional status at 12 months after surgery. Similar results were shown by Dziegielewski and colleagues, who reviewed a series of 81 patients who had TORS and found that patients had high levels of aesthetic, social and overall quality of life at 1 year after surgery.¹⁰² A recent randomized trial comparing primary TORS and primary radiotherapy (N = 34 per arm) showed comparable oncologic outcomes, differing side effect profile depending on treatment modality, and non–clinically meaningful differences in swallowing-related quality of life.⁶⁴

Complication rates have been found to be acceptably low following TORS for earlystage OPSCC. A recent systematic review found that, among patients undergoing TORS for early OPSCC, the rate of postoperative hemorrhage was 2.4%, the rate of neck hematoma was 0.4%, and the rate of pharyngocutaneous fistula was 2.5%.⁶¹ Other studies have found rates of postoperative hemorrhage ranging from 2.4% to 7.4%, which is similar to hemorrhage following palatine tonsillectomy (3.5%– 4.8%).^{61,65–69}

Advanced-Stage Oropharyngeal Cancers

Although most of the TORS literature focuses on outcomes of upfront surgery for early-stage OPSCC, there is also a growing body of evidence that TORS may have applications for upfront surgical management of more advanced disease. A 2011 study by Cohen and colleagues⁵⁸ reviewed 50 patients with OPSCC undergoing TORS and neck dissection, of whom 89% had stage 3 or stage 4 disease, and found 2-year overall survival and disease-specific survival for the entire cohort to be 81% and 93%, respectively. A recent National Cancer Database study examined 16,891 patients with stage 3 or 4 disease (excluding American Joint Committee on Cancer, Seventh Edition, T4b) and stratified by whether they received primary chemoradiation (N = 8123), surgery followed by radiation (N = 3519), or surgery followed by chemoradiation (N = 5249).⁷⁰ Patients receiving triple-modality therapy had the highest 3-year overall survival for surgery followed by radiation and 82% overall survival for primary chemoradiation; *P*<.01).⁷⁰

An additional benefit to upfront surgery in advanced OPSCC is the ability to obtain a pathologic specimen for restaging. In many cases, this leads to downstaging and reduces the needed radiation dose, and possibly avoids chemotherapy altogether.^{45,70,71} One study of 64 patients showed that upfront TORS resulted in the avoidance of chemotherapy in 34% of patients who presented with T3/T4 tumors, and another study of 76 patients showed that chemotherapy was able to be avoided in 46% of T3/T4 tumors.^{71,72}

Unknown Primary

Approximately 2% to 5% of all head and neck malignancies present as metastatic cervical squamous cell carcinoma with an unknown primary site.^{73,74} However, a traditional work-up involving history and physical examination, preoperative imaging studies, and selective operative endoscopy has been shown to identify primary malignancy in only 47% to 59% of patients.^{73,75} Primary identification is important because it helps to target therapy and also potentially reduce radiotherapy dosage, thus reducing radiation-related morbidity, and improve survival.^{76–78} Several institutions have described protocols generally involving TORS-assisted resection of ipsilateral palatine and possible lingual tonsillectomy with immediate frozen-section pathologic examination.^{79–82} If the primary is located, an oncologic procedure will proceed. If not, a contralateral diagnostic surgery will occur.⁷⁹ These TORS-assisted strategies

successfully identify the primary in 72% to 80% of cases.^{79–82} A full discussion of TORS for work-up of primary unknown malignancy, including a detailed surgical algorithm, can be found in a separate John R. de Almeida's article, "Role of TORS in the Work-Up of The Unknown Primary," of this series.

Salvage Oropharyngeal Surgery

Although surgery has been regarded as a salvage option following a partial response or local recurrence following primary radiotherapy or chemoradiotherapy for OPSCC, oncologic results have been disappointing. Five-year disease-free survival rates range from 19% to 22% in multiple large cohorts after traditional salvage surgery.^{83–85} In addition, major complication rates approach 50%, and include orocutaneous fistulae, neck abscess, systemic complications, and carotid rupture.^{84,85} In addition, traditional approaches to salvage oropharyngeal surgery are more invasive and often necessitate segmental mandibulectomy (44%–76%), total laryngectomy (6%–17%), and microvascular reconstruction (68%–82%).^{83–85} Permanent tracheostomy and gastrostomy tube rates following open salvage surgery have been found to vary between 7% and 15% and 4% and 65%, respectively.^{83–85}

The TORS approach to oropharyngeal salvage has shown encouraging early results compared with traditional techniques for salvage surgery. White and colleagues⁸⁶ described a 128-patient cohort of patients matched by TNM (tumor, node, metastasis) and evenly split between TORS and open salvage from a multi-institution study. TORS was found to significantly reduce rates of permanent gastrostomy (3% vs 31%) as well as reduce hospital length of stay (4 vs 8 days), blood loss (49 vs 331 mL), operative time (111 vs 350 minutes), and rates of positive margin (9% vs 29%).⁸⁶ Two-year disease-free survival was 74% and 43% in the TORS and open groups, respectively.⁸⁶ In a survival analysis of 30 patients who underwent TORS surgical salvage for OPSCC, Meulemans and colleagues⁸⁷ described a 2-year overall survival rate of 74% and disease-free survival of 76%. There are currently additional multi-institution cohort studies underway to further corroborate the benefits of TORS in the salvage setting.

Minor Salivary Gland Malignancies in the Oropharynx

Although minor salivary gland tumors vary greatly in their clinical behavior and appearance, most are malignant.⁸⁸ Standard therapy includes upfront surgery followed by pathology-driven adjuvant therapy because they tend to be radioresistant and therefore do poorly with radiation alone.^{89–91} Adjuvant radiation is recommended if the tumor is incompletely resected, is of an advanced stage, or if there are other adverse pathologic features.^{90–92}

Margin status is of the utmost importance, because negative margins have been shown to be an independent predictor for survival in numerous series.^{88,93–95} This finding poses a unique challenge to surgeons, because minor salivary tumors in the oropharynx have a propensity for submucosal growth and are located in a region that is traditionally difficult to access.⁸⁸ It is therefore unsurprising that efforts to resect tumors using traditional open approaches are associated with high rates of positive margins. For example, in a large series of 61 patients who underwent upfront open surgery for oropharyngeal minor salivary tumors (20 transoral, 4 transcervical, and 37 transmandibular), 28 (46%) patients had a positive margin on pathologic review.⁸⁸ In contrast, the TORS approach is well suited to the resection of oropharyngeal salivary malignancy because of improved access and visualization. Villaneueva and colleagues⁹⁶ reviewed a series of 10 patients who underwent TORS for oropharyngeal minor salivary gland tumors and reported that no patients in the cohort had a positive margin on final pathology. Similarly, Schoppy and colleagues⁹⁷ performed either

TORS or TLM on a group of 20 patients with oropharyngeal minor salivary tumors (18 TORS and 2 TLM) and reported a negative margin rate of 95%.

SURGICAL TECHNIQUES Preoperative Evaluation

Evaluation begins with detailed history and physical examination, with an emphasis on the presence and degree of trismus and assessment of cervical spine mobility.⁹⁸ Cross-sectional imaging is performed for staging, to assess resectability and to rule out internal carotid artery involvement.⁹⁸ An examination under anesthesia is performed to assess the extent of the tumor and whether there exists any contraindication for surgery (listed earlier).⁹⁸ In addition, patients are presented at a multidisciplinary tumor board to discuss options for treatment.

Radical Tonsillectomy

Setup: the nurse sits to the left of the patient, the robotic cart is positioned to the right of the patient, and the bedside surgical assistant sits at the patient's head. The patient is paralyzed. A tongue retraction suture is placed. A Crow-Davis mouth gag provides pharyngeal exposure and the patient is suspended via a Storz arm (Karl Storz, Tuttlingen, Germany). The 0° endoscope is placed in the central robotic arm and the lateral arms are loaded with a 5-mm monopolar cautery and Maryland retractor. The bedside assistant also has access to 2 suctions, a bayonet-style bipolar cautery, and an endoscopic clip applier with medium clip houses.^{48,98}

Step 1: an incision is made at the level of the pterygomandibular raphe through the buccal mucosa between the upper and lower molars using cautery. Step 2: dissection proceeds lateral to the constrictor muscles, bluntly dissecting the parapharyngeal fat pad laterally, identifying the pterygoid musculature laterally, and is carried down to the styloglossus and stylopharyngeus. Step 3: the soft palate and superior aspect of pharyngeal constrictors are transected through to the prevertebral fascia. Step 4: the constrictor muscles are bluntly elevated off the prevertebral fascia. Step 5: an index cut is made through the mucosa of the posterior pharyngeal wall. Step 6: a tongue base margin is taken by making an incision across the posterior floor of the mouth to the lateral tongue base down to the level of the vallecula. Step 7: care is taken to avoid transecting the lingual artery, but, if encountered, it is ligated with surgical clips. Step 8: the posterior pharyngeal wall is then resected from the vallecula up to the level of the soft palate along the previously made index cut. Care is taken on the lateral cuts as well as the pharyngeal cuts to protect the carotid arterial system.^{48,98} Step 9: pathologic analysis, final hemostasis, and reconstruction as required.^{48,98} Step 10: neck dissection occurs either concurrently or in a staged manner. A case example of TORS radical tonsillectomy is shown in Video 1.

Base of Tongue Resection

Setup: the setup for tongue base resection is similar to a radical tonsillectomy except an FK-WO retractor (with short Weinstein-O'Malley blade) is used and suspension is achieved with a Mayo stand. A Storz arm attaches to the bedside frame and supports the FK-WO retractor.^{49,98} The procedure is generally started with a 0° scope but is occasionally changed to a 30° scope later in the procedure.^{49,98}

Step 1: a pharyngeal cut is made in the tonsillar fossa. If the tumor is located in the glossotonsillar sulcus, a radical tonsillectomy will accompany the tongue base resection. If not, a small amount of tonsillar fossa is resected.^{49,98} Step 2: a partial horizontal tongue base mucosal cut is carried adjacent to retractor blade. Step 3: a midline

tongue base incision is made to an appropriate depth to account for tumor and margin. Step 4: the deep musculature transection is completed to an appropriate depth horizontally. Step 5: a lateral tongue base incision is made to bridge the pharyngeal cut and the lateral muscular cut. Step 7: the ipsilateral lingual artery and/or branches are identified and ligated with surgical clips. Step 8: the final dissection involves cutting through the remaining deep muscle and the underlying vallecular mucosa. Step 9: pathologic analysis, final hemostasis, and reconstruction as required. Step 10: neck dissection occurs either concurrently or in a staged manner.^{49,98} A case example of TORS tongue base resection is shown in Video 2.

SUMMARY

The dramatic increase in the incidence of OPSCC has been conclusively linked to HPV oncogenicity. These cancers, defined by a unique demographic profile and favorable outcomes, served as an impetus for the development of minimally invasive surgical techniques, including TORS. TORS has shown excellent oncologic and functional outcomes in the treatment of OPSCC and is also being increasingly used for other oropharyngeal indications.

DISCLOSURE

The authors have nothing to disclose.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10. 1016/j.otc.2020.07.007.

REFERENCES

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBO-CAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
- 2. Blot WJ, Devesa SS, McLaughlin JK, et al. Oral and pharyngeal cancers. Cancer Surv 1994;19-20:23–42.
- **3.** Franceschi S, Bidoli E, Herrero R, et al. Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. Oral Oncol 2000;36(1):106–15.
- 4. Hong AM, Grulich AE, Jones D, et al. Squamous cell carcinoma of the oropharynx in Australian males induced by human papillomavirus vaccine targets. Vaccine 2010;28(19):3269–72.
- Auluck A, Hislop G, Bajdik C, et al. Trends in oropharyngeal and oral cavity cancer incidence of human papillomavirus (HPV)-related and HPV-unrelated sites in a multicultural population: the British Columbia experience. Cancer 2010; 116(11):2635–44.
- Blomberg M, Nielsen A, Munk C, et al. Trends in head and neck cancer incidence in Denmark, 1978-2007: focus on human papillomavirus associated sites. Int J Cancer 2011;129(3):733–41.
- Braakhuis BJM, Visser O, Leemans CR. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral Oncol 2009;45(9):e85–9.
- 8. Mork J, Møller B, Dahl T, et al. Time trends in pharyngeal cancer incidence in Norway 1981-2005: a subsite analysis based on a reabstraction and recoding of registered cases. Cancer Causes Control 2010;21(9):1397–405.

- 9. Hammarstedt L, Lindquist D, Dahlstrand H, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. Int J Cancer 2006; 119(11):2620–3.
- 10. Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26(4):612–9.
- Reddy VM, Cundall-Curry D, Bridger MWM. Trends in the incidence rates of tonsil and base of tongue cancer in England, 1985-2006. Ann R Coll Surg Engl 2010;92(8):655–9.
- Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29(32): 4294–301.
- 13. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356(19):1944–56.
- 14. Ryerson AB, Peters ES, Coughlin SS, et al. Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998-2003. Cancer 2008;113(10 Suppl):2901–9.
- Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. Semin Oncol 2004;31(6): 744–54.
- 16. Marur S, D'Souza G, Westra WH, et al. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol 2010;11(8):781–9.
- Majchrzak E, Szybiak B, Wegner A, et al. Oral cavity and oropharyngeal squamous cell carcinoma in young adults: a review of the literature. Radiol Oncol 2014;48(1):1–10.
- Schnelle C, Whiteman DC, Porceddu SV, et al. Past sexual behaviors and risks of oropharyngeal squamous cell carcinoma: a case-case comparison. Int J Cancer 2017;140(5):1027–34.
- 19. D'Souza G, Agrawal Y, Halpern J, et al. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. J Infect Dis 2009;199(9):1263–9.
- 20. Pai SI, Westra WH. Molecular pathology of head and neck cancer: implications for diagnosis, prognosis, and treatment. Annu Rev Pathol 2009;4:49–70.
- 21. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100(4):261–9.
- 22. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363(1):24–35.
- 23. Bristow RG, Benchimol S, Hill RP. The p53 gene as a modifier of intrinsic radiosensitivity: implications for radiotherapy. Radiother Oncol 1996;40(3):197–223.
- Butz K, Geisen C, Ullmann A, et al. Cellular responses of HPV-positive cancer cells to genotoxic anti-cancer agents: repression of E6/E7-oncogene expression and induction of apoptosis. Int J Cancer 1996;68(4):506–13.
- 25. Lindel K, Beer KT, Laissue J, et al. Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. Cancer 2001;92(4):805–13.
- 26. Waldeyer W. Die Entwicklung der Carcinome. Arch Pathol Anat 1867;41: 470–522.
- Steckler RM, Shedd DP. General Grant: his physicians and his cancer. Am J Surg 1976;132(4):508–14.
- 28. Renehan A, Lowry JC. The oral tumours of two American presidents: what if they were alive today? J R Soc Med 1995;88(7):377–83.

- 29. Folz BJ, Silver CE, Rinaldo A, et al. An outline of the history of head and neck oncology. Oral Oncol 2008;44(1):2–9.
- **30.** Folz BJ, Ferlito A, Silver CE, et al. Neck dissection in the nineteenth century. Eur Arch Otorhinolaryngol 2007;264(5):455–60.
- **31.** Billroth T. Osteoplastiche Resectionen des Unterkiefers nach Eigener Methode. Arch Klin Chri 1862;2:651–7.
- 32. McGurk M, Goodger NM. Head and neck cancer and its treatment: historical review. Br J Oral Maxillofac Surg 2000;38(3):209–20.
- 33. Kocher T. Ueber Radicalheilung des Krebses. Dtsch Z Chir 1880;13:134-66.
- Holsinger FC, Weber RS. Swing of the surgical pendulum: a return to surgery for treatment of head and neck cancer in the 21st century? Int J Radiat Oncol Biol Phys 2007;69(2 Suppl):S129–31.
- **35.** Christopoulos E, Carrau R, Segas J, et al. Transmandibular approaches to the oral cavity and oropharynx. A functional assessment. Arch Otolaryngol Head Neck Surg 1992;118(11):1164–7.
- **36.** Stanley RB. Mandibular lingual releasing approach to oral and oropharyngeal carcinomas. Laryngoscope 1984;94(5 Pt 1):596–600.
- **37.** Vikram B, Strong EW, Shah J, et al. Elective postoperative radiation therapy in stages III and IV epidermoid carcinoma of the head and neck. Am J Surg 1980;140(4):580–4.
- **38.** Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999;91(24):2081–6.
- **39.** Pignon J-P, le Maître A, Maillard E, et al, MACH-NC Collaborative Group. Metaanalysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92(1):4–14.
- **40.** Caudell JJ, Schaner PE, Meredith RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;73(2):410–5.
- Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26(21):3582–9.
- 42. Huet PC. [Electrocoagulation in epitheliomas of the tonsils]. Ann Otolaryngol 1951;68(7):433–42.
- 43. Laccourreye O, Hans S, Ménard M, et al. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: II. An analysis of the incidence, related variables, and consequences of local recurrence. Arch Otolaryngol Head Neck Surg 2005;131(7):592–9.
- 44. Holsinger FC, McWhorter AJ, Ménard M, et al. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: I. Technique, complications, and functional results. Arch Otolaryngol Head Neck Surg 2005;131(7): 583–91.
- **45.** Haughey BH, Hinni ML, Salassa JR, et al. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. Head Neck 2011;33(12):1683–94.
- **46.** Hockstein NG, O'Malley BW, Weinstein GS. Assessment of intraoperative safety in transoral robotic surgery. Laryngoscope 2006;116(2):165–8.
- **47.** Weinstein GS, O'malley BW, Hockstein NG. Transoral robotic surgery: supraglottic laryngectomy in a canine model. Laryngoscope 2005;115(7):1315–9.
- **48.** Weinstein GS, O'Malley BW, Snyder W, et al. Transoral robotic surgery: radical tonsillectomy. Arch Otolaryngol Head Neck Surg 2007;133(12):1220–6.

- **49.** O'Malley BW, Weinstein GS, Snyder W, et al. Transoral robotic surgery (TORS) for base of tongue neoplasms. Laryngoscope 2006;116(8):1465–72.
- Mandapathil M, Duvvuri U, Güldner C, et al. Transoral surgery for oropharyngeal tumors using the Medrobotics(®) Flex(®) System - a case report. Int J Surg Case Rep 2015;10:173–5.
- Persky MJ, Issa M, Bonfili JR, et al. Transoral surgery using the Flex Robotic System: Initial experience in the United States. Head Neck 2018;40(11):2482–6.
- Holsinger FC, Magnuson JS, Weinstein GS, et al. A next-generation single-port robotic surgical system for transoral robotic surgery: results from prospective nonrandomized clinical trials. JAMA Otolaryngol Head Neck Surg 2019. https://doi.org/10.1001/jamaoto.2019.2654.
- 53. Weinstein GS, O'Malley BW, Magnuson JS, et al. Transoral robotic surgery: a multicenter study to assess feasibility, safety, and surgical margins. Laryngo-scope 2012;122(8):1701–7.
- 54. Cracchiolo JR, Roman BR, Kutler DI, et al. Adoption of transoral robotic surgery compared with other surgical modalities for treatment of oropharyngeal squamous cell carcinoma. J Surg Oncol 2016;114(4):405–11.
- 55. Lam JS, Scott GM, Palma DA, et al. Development of an online, patient-centred decision aid for patients with oropharyngeal cancer in the transoral robotic surgery era. Curr Oncol 2017;24(5):318–23.
- **56.** Weinstein GS, O'Malley BW, Rinaldo A, et al. Understanding contraindications for transoral robotic surgery (TORS) for oropharyngeal cancer. Eur Arch Otorhinolaryngol 2015;272(7):1551–2.
- 57. Loevner LA, Learned KO, Mohan S, et al. Transoral robotic surgery in head and neck cancer: what radiologists need to know about the cutting edge. Radiographics 2013;33(6):1759–79.
- 58. Cohen MA, Weinstein GS, O'Malley BW, et al. Transoral robotic surgery and human papillomavirus status: Oncologic results. Head Neck 2011;33(4):573–80.
- Moore EJ, Olsen SM, Laborde RR, et al. Long-term functional and oncologic results of transoral robotic surgery for oropharyngeal squamous cell carcinoma. Mayo Clin Proc 2012;87(3):219–25.
- **60.** de Almeida JR, Li R, Magnuson JS, et al. Oncologic Outcomes After Transoral Robotic Surgery: A Multi-institutional Study. JAMA Otolaryngol Head Neck Surg 2015;141(12):1043–51.
- **61.** de Almeida JR, Byrd JK, Wu R, et al. A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review. Laryngoscope 2014;124(9):2096–102.
- 62. Leonhardt FD, Quon H, Abrahão M, et al. Transoral robotic surgery for oropharyngeal carcinoma and its impact on patient-reported quality of life and function. Head Neck 2012;34(2):146–54.
- **63.** Kelly K, Johnson-Obaseki S, Lumingu J, et al. Oncologic, functional and surgical outcomes of primary Transoral Robotic Surgery for early squamous cell cancer of the oropharynx: a systematic review. Oral Oncol 2014;50(8):696–703.
- 64. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. Lancet Oncol 2019. https://doi.org/10.1016/S1470-2045(19)30410-3.
- 65. Asher SA, White HN, Kejner AE, et al. Hemorrhage after transoral roboticassisted surgery. Otolaryngol Head Neck Surg 2013;149(1):112–7.

- Parhar HS, Gausden E, Patel J, et al. Analysis of readmissions after transoral robotic surgery for oropharyngeal squamous cell carcinoma. Head Neck 2018; 40(11):2416–23.
- 67. Stokes W, Ramadan J, Lawson G, et al. Bleeding complications after transoral robotic surgery: a meta-analysis and systematic review. Laryngoscope 2020. https://doi.org/10.1002/lary.28580.
- **68.** Lowe D, van der Meulen J, Cromwell D, et al. Key messages from the National Prospective Tonsillectomy Audit. Laryngoscope 2007;117(4):717–24.
- 69. Bhattacharyya N, Kepnes LJ. Revisits and postoperative hemorrhage after adult tonsillectomy. Laryngoscope 2014;124(7):1554–6.
- 70. Roden DF, Schreiber D, Givi B. Triple-modality treatment in patients with advanced stage tonsil cancer. Cancer 2017;123(17):3269–76.
- 71. Hurtuk A, Agrawal A, Old M, et al. Outcomes of transoral robotic surgery: a preliminary clinical experience. Otolaryngol Head Neck Surg 2011;145(2):248–53.
- 72. Gildener-Leapman N, Kim J, Abberbock S, et al. Utility of up-front transoral robotic surgery in tailoring adjuvant therapy. Head Neck 2016;38(8):1201–7.
- Waltonen JD, Ozer E, Hall NC, et al. Metastatic carcinoma of the neck of unknown primary origin: evolution and efficacy of the modern workup. Arch Otolaryngol Head Neck Surg 2009;135(10):1024–9.
- 74. Schmalbach CE, Miller FR. Occult primary head and neck carcinoma. Curr Oncol Rep 2007;9(2):139–46.
- Keller F, Psychogios G, Linke R, et al. Carcinoma of unknown primary in the head and neck: comparison between positron emission tomography (PET) and PET/CT. Head Neck 2011;33(11):1569–75.
- Grewal AS, Rajasekaran K, Cannady SB, et al. Pharyngeal-sparing radiation for head and neck carcinoma of unknown primary following TORS assisted workup. Laryngoscope 2020;130(3):691–7.
- Haas I, Hoffmann TK, Engers R, et al. Diagnostic strategies in cervical carcinoma of an unknown primary (CUP). Eur Arch Otorhinolaryngol 2002;259(6): 325–33.
- Davis KS, Byrd JK, Mehta V, et al. Occult Primary Head and Neck Squamous Cell Carcinoma: Utility of Discovering Primary Lesions. Otolaryngol Head Neck Surg 2014;151(2):272–8.
- Hatten KM, O'Malley BW, Bur AM, et al. Transoral Robotic Surgery-Assisted Endoscopy With Primary Site Detection and Treatment in Occult Mucosal Primaries. JAMA Otolaryngol Head Neck Surg 2017;143(3):267–73.
- **80.** Patel SA, Magnuson JS, Holsinger FC, et al. Robotic surgery for primary head and neck squamous cell carcinoma of unknown site. JAMA Otolaryngol Head Neck Surg 2013;139(11):1203–11.
- 81. Fu TS, Foreman A, Goldstein DP, et al. The role of transoral robotic surgery, transoral laser microsurgery, and lingual tonsillectomy in the identification of head and neck squamous cell carcinoma of unknown primary origin: a systematic review. J Otolaryngol Head Neck Surg 2016;45(1):28.
- Geltzeiler M, Doerfler S, Turner M, et al. Transoral robotic surgery for management of cervical unknown primary squamous cell carcinoma: Updates on efficacy, surgical technique and margin status. Oral Oncol 2017;66:9–13.
- Zafereo ME, Hanasono MM, Rosenthal DI, et al. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. Cancer 2009;115(24):5723–33.

- Righini C-A, Nadour K, Faure C, et al. Salvage surgery after radiotherapy for oropharyngeal cancer. Treatment complications and oncological results. Eur Ann Otorhinolaryngol Head Neck Dis 2012;129(1):11–6.
- 85. Patel SN, Cohen MA, Givi B, et al. Salvage surgery for locally recurrent oropharyngeal cancer. Head Neck 2016;38(Suppl 1):E658–64.
- **86.** White H, Ford S, Bush B, et al. Salvage surgery for recurrent cancers of the oropharynx: comparing TORS with standard open surgical approaches. JAMA Otolaryngol Head Neck Surg 2013;139(8):773–8.
- 87. Meulemans J, Vanclooster C, Vauterin T, et al. Up-front and Salvage Transoral Robotic Surgery for Head and Neck Cancer: A Belgian Multicenter Retrospective Case Series. Front Oncol 2017;7:15.
- Iyer NG, Kim L, Nixon IJ, et al. Factors predicting outcome in malignant minor salivary gland tumors of the oropharynx. Arch Otolaryngol Head Neck Surg 2010;136(12):1240–7.
- 89. Guzzo M, Locati LD, Prott FJ, et al. Major and minor salivary gland tumors. Crit Rev Oncol Hematol 2010;74(2):134–48.
- **90.** Mendenhall WM, Morris CG, Amdur RJ, et al. Radiotherapy alone or combined with surgery for salivary gland carcinoma. Cancer 2005;103(12):2544–50.
- 91. Parsons JT, Mendenhall WM, Stringer SP, et al. Management of minor salivary gland carcinomas. Int J Radiat Oncol Biol Phys 1996;35(3):443–54.
- **92.** Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg 1986;8(3):177–84.
- **93.** Copelli C, Bianchi B, Ferrari S, et al. Malignant tumors of intraoral minor salivary glands. Oral Oncol 2008;44(7):658–63.
- **94.** Carrillo JF, Maldonado F, Carrillo LC, et al. Prognostic factors in patients with minor salivary gland carcinoma of the oral cavity and oropharynx. Head Neck 2011;33(10):1406–12.
- **95.** Hay AJ, Migliacci J, Karassawa Zanoni D, et al. Minor salivary gland tumors of the head and neck-Memorial Sloan Kettering experience: Incidence and outcomes by site and histological type. Cancer 2019;125(19):3354–66.
- **96.** Villanueva NL, de Almeida JR, Sikora AG, et al. Transoral robotic surgery for the management of oropharyngeal minor salivary gland tumors. Head Neck 2014; 36(1):28–33.
- **97.** Schoppy DW, Kupferman ME, Hessel AC, et al. Transoral endoscopic head and neck surgery (eHNS) for minor salivary gland tumors of the oropharynx. Cancers Head Neck 2017;2:5.
- **98.** Weinstein GS, O'Malley BW. TransOral robotic surgery (TORS). San Diego (CA): Plural Pub; 2012.
- **99.** Sharma A, Patel S, Baik FM, et al. Survival and gastrostomy prevalence in patients with oropharyngeal cancer treated with transoral robotic surgery vs chemoradiotherapy. JAMA Otolaryngol Head Neck Surg 2016;142(7):691–7.
- Moore EJ, Van Abel KM, Price DL, et al. Transoral robotic surgery for oropharyngeal carcinoma: Surgical margins and oncologic outcomes. Head Neck 2018; 40(4):747–55.
- **101.** Dhanireddy B, Burnett NP, Sanampudi S, et al. Outcomes in surgically resectable oropharynx cancer treated with transoral robotic surgery versus definitive chemoradiation. Am J Otolaryngol 2019;40(5):673–7.
- 102. Dziegielewski PT, Teknos TN, Durmus K, et al. Transoral robotic surgery for oropharyngeal cancer: long-term quality of life and functional outcomes. JAMA Otolaryngol Head Neck Surg 2013;139(11):1099–108.

- **103.** Achim V, Bolognone RK, Palmer AD, et al. Long-term functional and quality-oflife outcomes after transoral robotic surgery in patients with oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 2018;144(1):18–27.
- 104. Sethia R, Yumusakhuylu AC, Ozbay I, et al. Quality of life outcomes of transoral robotic surgery with or without adjuvant therapy for oropharyngeal cancer. Laryngoscope 2018;128(2):403–11.
- 105. Van Abel KM, Quick MH, Graner DE, et al. Outcomes following TORS for HPVpositive oropharyngeal carcinoma: PEGs, tracheostomies, and beyond. Am J Otolaryngol 2019;40(5):729–34.