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Positive Margins by Oropharyngeal Subsite in Transoral Robotic Surgery for T1/T2 Squamous Cell Carcinoma

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Abstract

Objective—To compare positive margin rates between the 2 most common subsites of oropharyngeal transoral robotic surgery (TORS), the base of tongue (BOT) and the tonsil, as well as identify preoperative imaging characteristics that predispose toward positive margins.

Study Design—Case series with chart review.

Setting—Tertiary care referral center.

Subjects and Methods—We compared the final and intraoperative positive margin rate between TORS resections for tonsil and BOT oropharyngeal squamous cell carcinoma (OPSCC), as well as the effect of margins on treatment. A blinded neuroradiologist examined the preoperative imaging of BOT tumors to measure their dimensions and patterns of spread and provided a prediction of final margin results.

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Author Contributions

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Results—Between January 2010 and May 2016, a total of 254 patients underwent TORS for OPSCC. A total of 140 patients who underwent TORS for T1/T2 OPSCC met inclusion criteria. A final positive margin is significantly more likely for BOT tumors than tonsil tumors (19.6% vs 4.5%, respectively, $P = .004$) and likewise for intraoperative margins of BOT and tonsil tumors (35.3% vs 12.4%, respectively; $P = .002$). A positive final margin is 10 times more likely to receive chemoradiation compared to a negative margin, controlling for extracapsular spread and nodal status (odds ratio, 9.6; 95% confidence interval, 1.6–59.6; $P = .02$). Preoperative imaging characteristics and subjective radiologic examination of BOT tumors did not correlate with final margin status.

Conclusion—Positive margins are significantly more likely during TORS BOT resections compared to tonsil resections. More research is needed to help surgeons predict which T1/T2 tumors will be difficult to completely extirpate.

Keywords

TORS; margins; oropharyngeal SCC; margin status; radical tonsillectomy; BOT resection

Transoral robotic surgery (TORS) for the primary treatment of oropharyngeal squamous cell carcinoma (OPSCC) is increasingly used in patients with T1 and T2 primary tumors.¹ TORS was approved by the US Food and Drug Administration (FDA) in 2009, around the same time researchers and clinicians recognized that the new dominant cause of OPSCC was human papillomavirus (HPV) related.² HPV positivity portends a better prognosis and is associated with lower T-stage, which improves likelihood of resectability.^{3,4} Coincidentally, robot-assisted surgical technology has improved over the same time period, allowing patients who had previously been treated with radiation-based treatment to be treated surgically, with the goal of avoiding long-term radiation-associated toxicity.⁵ TORS is commonly used for the discovery of an unknown primary and extirpation of T1/T2 OPSCC, although some surgeons will use robotics in the resection of larger oropharyngeal tumors, as well as for laryngeal and hypopharyngeal tumors. The oncologic outcomes after TORS OPSCC resections are excellent, and evidence suggests that the intermediate-term quality-of-life outcomes are superior compared with radiation and chemoradiation, but long-term data are lacking.^{6,7} Given the excellent prognosis of these HPV-related cancers after primary surgical treatment, oncologists are reevaluating the indications for, and intensity of, adjuvant treatments.⁸

Despite the potential advantages of a surgery-first treatment paradigm, there is a risk of obtaining positive margins that generally risk-stratify the patient to adjuvant chemoradiotherapy (CRT).⁹ In these cases, adjuvant CRT condemns patients to trimodality treatment when upfront CRT alone would likely have achieved a similar oncologic outcome without exposing the patient to potential increased risk of functional deficits or side effects from surgical treatment. Furthermore, while there are multiple randomized trials investigating paths toward reduced-dose adjuvant treatment, none contain an algorithm to reduce treatment for patients with positive pathologic margins. To that end, surgeons are rightfully cautious about attempting resection where risk of positive margins is high.

To reduce the rate of positive margins in TORS resections, surgeons should be aware of any tumor subsites or physical characteristics that predispose to positive margins and thus portend a worse surgical outcome. While there are sufficient data regarding margin rates after TORS, currently no data suggest a difference in positive margin rates by oropharyngeal subsite. One population-level analysis found the positive margin rate of 877 patients to be 20.2% (82.5% of these were pathologically T1 or T2).¹⁰ A recent single-institution study found a positive margin rate of 21% for specifically T1 and T2 tumors, but as with all previous studies, the authors did not evaluate the difference by subsite.¹¹ Regarding these tumors' physical characteristics, no study has evaluated preoperative imaging to identify features that may predispose toward positive margins.

The 2 most common subsites for OPSCC are the lingual tonsil, which we will refer to as the base of tongue (BOT), and the palatine tonsil, which we will refer to as the tonsil.¹² Our experience suggests that exposure and dissection are more difficult in the BOT than the tonsil. We therefore hypothesized that there is a higher positive margin rate in the BOT than the tonsil. In addition, we looked to see if margin status affected the use of adjuvant radiotherapy (RT) or CRT as well as posttreatment disease status. Finally, we examined preoperative imaging to determine if objective and subjective features could accurately predict margin status.

Methods

This is a retrospective review of all OPSCCs treated with TORS at the University of Pittsburgh between January 2010 and May 2016. Approval was obtained from the University of Pittsburgh Institutional Review Board. Inclusion criteria were tonsil/BOT primaries, which were clinically staged T1 or T2 and whose margins were able to be assessed on retrospective review (ie, not biopsy). Both HPV+ and HPV– patients were included. Patients not treated for curative intent or those with grossly positive margins were excluded. Patients with margin status that was indeterminate were excluded as were those with unknown primary at the time of resection. Patients who were being treated for recurrent OPSCC were similarly excluded. We opted to evaluate only those patients with T1 and T2 tumors of the BOT and tonsil as these are the most common tumors treated with TORS. The da Vinci surgical robotic system (Intuitive Surgical, Sunnyvale, California) was used for all resections by the 3 senior authors (U.D., R.L.F., and S.K.). Figure 1 shows a flow diagram of patient selection.

Clinical records were queried for demographic, staging, and treatment data. Our primary outcome measure was final margin status (positive vs negative). Margin status was assigned based on review of the pathology report by the authors.

Specimens were sent to pathology fresh. Margins were considered positive if there was tumor “at the ink.” Margins were considered negative if either the primary specimen or field margins were negative or if chased margins were negative at final resection during the primary procedure. Patients who had a second procedure to clear positive margins were considered to have positive margins. Close margins were considered negative.

It is common for robotic surgeons to send the resection specimen for intraoperative pathologic consultation (frozen-section analysis) to evaluate the margins, with the goal of further resection if any margin is determined to be positive. Therefore, our secondary outcome measure is intraoperative margin status, which is defined as negative (negative main specimen or field margins) or positive (positive frozen section necessitating further resection) regardless of final margin status.

Patients were stratified by primary location (BOT vs tonsil). If the tumor involved both the BOT and tonsil, it was assigned to the subsite that was more involved, either by review of operative report or pathologic report. Baseline demographics and staging were compared between the 2 groups using χ^2 tests and t tests. Final and intraoperative margin rate was compared between the 2 groups using χ^2 tests. Logistic regression models were used to predict final and intraoperative margins with tumor location, pathologic T-stage, and HPV status as independent variables.

The use and dose of adjuvant RT or CRT between the 2 groups were compared using a logistic regression model, controlling for lymph node extracapsular spread (ECS) and number of metastatic lymph nodes (0–4 or greater than 4), 2 common indications for adjuvant therapy or intensification. The nonparametric Wilcoxon Mann-Whitney test was used to assess the relationship of intraoperative and final margin status with adjuvant radiation dose.

A fellowship-trained neuroradiologist (T.J.R.) blinded to resection outcomes evaluated the cross-sectional computed tomography (CT) imaging of each BOT tumor to determine if there were preoperative tumor characteristics predictive of margin results. Only patients with postcontrast CT scans were included. If the presurgical exam was magnetic resonance imaging (MRI), a noncontrast image associated with a positron emission tomography (PET) scan, or if the imaging could not be located, the patients were excluded. In addition, patients were excluded if the tumor was occult on CT. The neuroradiologist recorded transverse (TR), anteroposterior (AP), and craniocaudal (CC) dimensions of each tumor. In addition, the radiologist's perception of each tumor's pattern of spread was recorded: superficial (spreads along the surface of the BOT in a fashion similar to lingual tonsillar tissue), exophytic (protrudes from the base of tongue beyond the margin of normal BOT tissue into space of the airway), or deep (extends anterior to the margin of expected normal BOT tissue) (see Figure 2). Finally, the neuroradiologist predicted final margin status (positive, negative, equivocal).

Results

From 2010 to 2016, a total of 254 patients underwent TORS for OPSCC, and 114 patients were excluded (11 patients for noncurative intent resection, 16 patients for TORS for recurrent OPSCC, 69 for TORS for unknown primary, 14 for pT3/T4 OPSCC, 4 for nontonsil/BOT subsite). Thus, 140 patients met inclusion criteria and were available for analysis. Baseline patient characteristics are shown in Table 1. Eighty percent of these patients were male, and the mean age was 58 years. Fifty-one patients (36.4%) had tumors of the BOT, and 89 patients (63.6%) had tumors of the tonsil. Of the 140 patients, 123

(87.8%) tested positive for p16. There were no significant differences between the 2 groups at baseline. Median follow-up from the time of surgery was 27 months, with a range from less than 1 month to 80 months.

Regarding the primary objective, a final positive margin after TORS is significantly more likely for a BOT tumor than a tonsil tumor. Overall final positive margin rate was 10.0%. While 10 of the 51 BOT (19.6%) resections resulted in a positive margin, only 4 of the 89 (4.5%) tonsil resections had a positive margin ($P = .004$). After controlling for the effects of pathologic T-stage and HPV status, the odds of having final positive margins are 6.6 times higher in BOT tumor resections than tonsil tumor resections (95% confidence interval [CI], 1.8–24.3; $P = .005$). Thus, we are unable to exclude the null hypothesis.

Our secondary outcome assessed for intraoperative margin status. Our data suggest that positive intraoperative margins are positive more frequently in BOT tumor resections than tonsil tumor resections, necessitating further resection to obtain negative final margins (35.3% of BOT cases vs 12.4% of tonsil cases, $P = .002$). After controlling for the effects of pathologic T-stage and HPV status, the odds of having positive intraoperative margins are 3.9 (95% CI, 1.6–9.7) times higher in BOT subjects than tonsil subjects ($P = .003$).

Six of the 10 positive BOT tumor resections had positive margins at more than 1 site. Among the specimens with positive margins, the most commonly involved was the deep margin (8/10). Three were positive at the lateral margin, 2 at the posterior margin, 1 at the medial margin, and 1 at the inferior margin.

After controlling for ECS and number of lymph node metastases (0–4 or more than 4), patients with intraoperative and final positive margins were 5 and 10 times more likely to have received adjuvant CRT, respectively, than if those margins were negative. We did not find a statistically significant difference in radiation dose between subjects with and without positive intraoperative or final margins.

A neuroradiologist evaluated 38 of 51 BOT patients; 9 patients were excluded due to noncontrast CTs, 3 due to CT-occult tumors, and 1 due to an unavailable preoperative CT. Tumor characteristics can be seen in Tables 2 and 3. TR, AP, and CC measurements did not correlate to final or intraoperative margin status. Likewise, subjective judgment regarding pattern of spread and margin expectations did not correlate to final or intraoperative margin status (see Figure 1).

Discussion

Positive margins are significantly more likely during TORS resection of BOT tumors vs tonsil tumors on both permanent pathologic analysis and frozen section. As technology improves, so too must patient selection to provide optimal outcomes for patients with OPSCC. In current accepted practice and according to the National Comprehensive Cancer Network guidelines, both upfront chemoradiation and/or surgery with risk-stratified adjuvant therapy are acceptable treatment algorithms.^{9,13} However, as can be seen in our cohort as well as in other studies, patients who undergo a surgery-first modality with subsequent positive margins are more likely to undergo adjuvant chemoradiation.^{9,13} Thus, surgical

resection with a goal of decreasing the dose of, or need for, adjuvant treatment will instead result in an overall increased amount of total treatment if the margin of resection is positive. As such, it is important to select surgical patients who have an excellent chance for a resection with negative margins.

Comparing definitive treatment with TORS and risk-stratified adjuvant therapy to primary radiation-based treatment shows that patients undergoing primary surgery have improved quality-of-life (QOL) outcomes while maintaining similar oncologic outcomes. In addition, an upfront surgical approach is reported to obviate the need for adjuvant treatment in up to 50% to 72% of stage I or II tumors, leading to improved QOL.^{14,15} Hurtuk et al¹⁶ prospectively evaluated 64 patients undergoing TORS and neck dissection and found that the addition of adjuvant treatment reduced eating, social, and overall QOL scores at 1 year. Ling et al¹⁷ looked at 92 patients who underwent TORS plus or minus adjuvant treatment and found that patients who underwent adjuvant treatment had a worse taste-related QOL at 1 year and worse saliva-related QOL at 2 years posttreatment.

Specifically, the avoidance of adjuvant chemotherapy treatment is an important benefit of primary TORS. A recent study looked at 76 patients who underwent TORS resection of OPSCC with the goal of evaluating how upfront surgery helps to tailor adjuvant treatment. It was found that 76% of stage I and II patients and 46% of stage III/IV patients were able to avoid chemotherapy as a result of primary TORS treatment. Ninety-one percent of these patients had T1 or T2 disease, which is similar to the population in this study.¹⁴ This same study cites positive margins as a statistically significant predictor of adjuvant chemotherapy, which is what our data show as well. The advantage of avoiding chemotherapy is reduced systemic toxicity and improved posttreatment swallowing function, an important QOL metric.^{18,19}

Given that surgery is an acceptable treatment option due to similar oncologic outcomes and improved QOL outcomes, it is clear that avoiding incomplete extirpation and subsequent chemoradiation (trimodality treatment) is critically important. A recent query of 3071 patients in the National Cancer Database that evaluated TORS resection of oropharyngeal tumors found an overall positive margin rate of 14.2%, which is slightly higher than our overall positive margin rate of 10.0%.¹ This study went on to show that high-volume centers were significantly more likely to obtain negative margins. However, this study did not stratify the margin outcomes by subsite or T-stage, which we think is necessary to guide appropriate patient selection. To our knowledge, no previous studies have stratified positive margins by subsite and T-stage.

Our data suggest that the BOT is a more difficult oropharyngeal subsite than the palatine tonsil to obtain negative margins for T1/T2 primarily resected OPSCC. This is in keeping with our null hypothesis based on clinical experience. Furthermore, the deep margin is the hardest to clear, as it was a site of positivity in two-thirds of incomplete BOT tumor resections, which has also been reported elsewhere.²⁰ This fact makes intuitive sense as this is the only BOT margin without a visual cue as to the extent of cancer. In contrast, the deep margin on tonsil tumor resection is consistent: when parapharyngeal fat is exposed, the deep margin is satisfied. Also, the da Vinci (Intuitive Surgical) has limited tactile feedback,

preventing the surgeon from using haptic cues to assist in complete extirpation.²¹ In addition, a BOT tumor is surrounded by cryptic lingual tonsillar mucosa, as opposed to the smooth mucosa of the tonsillar pillars and soft palate that provide clues to the mucosal extent of the tumor. Accordingly, we found that intraoperative margin revisions resulting from frozen-section analysis were about 3 times more likely for BOT tumors than tonsil tumors. These intraoperative revisions brought the final margin positivity down to 19.6% from 35.3%.

To our knowledge, there is no prior study looking for tumor characteristics that can predict a relatively high likelihood of positive margins. Given that the majority of BOT margin positivity is at the deep margin, we expected those tumors with a larger AP dimension and/or a deep pattern of growth on imaging would correlate with positive margins.²⁰ While this correlation was not present in our data, the power of this portion of the study was low given our focus on the BOT subset. In addition, because most of our patients received preoperative CTs, we used this modality for this study. However, magnetic resonance imaging (MRI) offers better soft tissue contrast and may demonstrate tumor margins better. Future studies should examine whether preoperative MRIs provide better accuracy in predicting margin status, which would help justify its more expensive cost in working up these patients.

This is the first study to attempt to delineate the characteristics of oropharyngeal tumors that herald an increased potential for positive margins after TORS resection. As we learn more about the excellent prognosis of HPV-related tumors, effort should be directed toward reducing the morbidity of treatment. One way to do this is to improve the selection of surgical candidates. Given a substantial percentage of BOT tumors are resected with positive margins, research should focus on the characteristics of this subset of tumors that will help predict complete resection.

An inherent limitation of this study is its retrospective nature. For example, some consider the glossotonsillar sulcus to be a distinct subsite, but we were unable to reliably assign patients into this category from the information available. Another consideration is that resections were performed by multiple surgeons who have varied techniques and who may have differences in opinion regarding resectability. Finally, our results regarding a tumor's preoperative imaging characteristics and margin status have low power due to focusing on the BOT subset.

Conclusion

Positive margins are significantly more likely during TORS resection of BOT tumors vs tonsil tumors, which increases the risk of the need for adjuvant chemoradiation. Efforts should continue to both improve our ability to completely extirpate these tumors and identify BOT tumor characteristics that may predict positive margins.

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Figure 1.

Flow diagram showing inclusion and exclusion criteria for patient population. BOT, base of tongue; OPSCC, oropharyngeal squamous cell carcinoma; TORS, transoral robotic surgery.

Figure 2.
From left to right, example of superficial, exophytic, and deep patterns of base of tongue tumor growth.

Table 1

Demographic Information.

Characteristic	Primary Surgery				P Value
	BOT (n = 51)		Tonsil (n = 89)		
	n	%	n	%	
Sex					.16
Female	7	13.73	21	23.60	
Male	44	86.27	68	76.40	
Age, y					.79
No.	51		89		
Mean (SD)	58 (13.4)		58 (9.8)		
Median (IQR)	59 (53–66)		57 (50–64)		
Race					1.0
African American	1	1.96	3	3.37	
White	50	98.04	85	95.51	
Unknown	.	.	1	1.12	
Tobacco status					.24
Current	10	19.61	25	28.09	
Former	19	37.25	37	41.57	
Never	22	43.14	26	29.21	
Pathologic T-stage					.10
1	28	54.90	36	40.45	
2	23	45.10	53	59.55	
Pathologic N-stage					.18
0	6	11.76	21	23.60	
1	13	25.49	14	15.73	
2A	8	15.69	13	14.61	
2B	15	29.41	33	37.08	
2C	5	9.80	3	3.37	
3	1	1.96	1	1.12	

Characteristic	Primary Surgery						P Value
	BOT (n = 51)		Tonsil (n = 89)				
	n	%	n	%			
x	3	5.88	4	4.49			
PNI						.77	
No	41	80.39	73	82.02			
Yes	9	17.65	14	15.73			
Unknown	1	1.96	2	2.25			
ALI						.59	
No	25	49.02	43	48.31			
Yes	16	31.37	34	38.20			
Unknown	10	19.61	12	13.48			
HPV status						.051	
Positive	49	96	74	83			
Negative	2	4	14	16			
Unknown			1	1			
Final margins						.004	
Negative	40	78.4	85	95.51			
Positive	10	19.6	4	4.49			
Unknown	1	1.96					
Intraoperative margins						.002	
Negative	32	62.75	73	82.02			
Positive	18	35.29	11	12.36			
Unknown	1	1.96	5	5.62			

Abbreviations: ALI, angiolymphatic invasion; BOT, base of tongue; HPV, human papillomavirus; IQR, interquartile range; PNI, perineural invasion; SD, standard deviation.

Table 2

Tumor Characteristics Correlated with Final Margins.

Characteristic	Final Margins Positive	Final Margins Negative	P Value
TR			
No.	8	29	.78
Mean (SD)	1.82 (0.37)	1.94 (0.59)	
AP			
No.	8	29	.82
Mean (SD)	1.42 (0.85)	1.32 (0.70)	
CC			
No.	8	29	.90
Mean (SD)	1.87 (0.43)	1.96 (0.85)	
Pattern of spread, No. (%)			
Superficial	4 (50)	20 (69)	.41
Deep	4 (50)	9 (31)	
Expected positive margins? No. (%)			
Yes	4 (50)	7 (24)	.41
No	4 (50)	20 (69)	
Equivocal		2 (7)	

Abbreviations: AP, anteroposterior; CC, craniocaudal; SD, standard deviation; TR, transverse.

Table 3

Tumor Characteristics Correlated with Intraoperative Margins.

Characteristic	Intraoperative Margins Positive	Intraoperative Margins Negative	P Value
TR			
No.	14	23	.64
Mean (SD)	1.84 (0.50)	1.96 (0.58)	
AP			
No.	14	23	.35
Mean (SD)	1.20 (0.71)	1.42 (0.73)	
CC			
No.	14	23	.24
Mean (SD)	1.72 (0.50)	2.07 (0.88)	
Pattern of spread, No. (%)			
Superficial	9 (64)	15 (65)	1.0
Deep	5 (36)	8 (35)	
Expected positive margins? No. (%)			
Yes	5 (36)	6 (26)	.54
No	9 (64)	15 (65)	
Equivocal		2 (9)	

Abbreviations: AP, anteroposterior; CC, craniocaudal; SD, standard deviation; TR, transverse.