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ORIGINAL RESEARCH

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Clarification of the margin status by the multidisciplinary tumor board following transoral robotic surgery for p16 positive oropharyngeal squamous cell carcinoma

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Abstract

Objectives: Margin status interpretation following transoral robotic surgery (TORS) for oropharyngeal squamous cell carcinoma (OPSCC) is challenging. This study aims to assess the discrepancy between status of margins as reported by the pathologist versus as determined by multi-disciplinary team review (MDTB).

Methods: A retrospective study of 57 patients with OPSCC who underwent TORS from January 2010 to December 2016 was conducted. Our primary outcome measure was the discrepancy between the surgical specimen margins as described in the pathology report versus final margin status that was determined after the multi-disciplinary team discussion. Fisher's exact test was used.

Results: Based on the pathologist-report, 29 subjects (51%) had positive margins, compared to 2 (4%) after multi-disciplinary team discussion. Receipt of chemotherapy correlated with final margin status as determined by MDTB, not with initial main specimen margins ($p = .02$ and $p = .08$, respectively). With a median follow up of 28.4 months, two subjects (4%) had loco-regional recurrence.

Conclusion: Following TORS, there was a significant discrepancy between status of margins as reported by the pathologist versus as determined by MDTB review. Chemotherapy was avoided in 93.1% of cases that were originally reported as positive margins by the pathologist with an acceptably low recurrence rate.

Level of evidence: 4.

KEYWORDS

head and neck cancer, margins, margin status, oropharyngeal squamous cell carcinoma, robotic surgery, TORS, transoral robotic assisted surgery

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1 | INTRODUCTION

Randomized clinical trials of advanced head and neck cancer concluded that cisplatin chemotherapy given post operatively in patients with positive margins and/or extra capsular spread significantly improves overall survival, albeit with increased toxicity (RTOG1016, European study).[1–3] With the advent of transoral surgery, there has been a shift from non-surgical to surgical management of early stage oropharyngeal squamous cell carcinoma. In the past decade, transoral robotic surgery (TORS) has grown in popularity. There is a general agreement about the importance of clear margins and that failure to eradicate tumors at the primary site is potentially the single largest cause of mortality.[4,5] However, the complex tortuous anatomy of the tongue base, the lack of tactile feedback with TORS and the anatomical limitations as in the parapharyngeal space make it challenging to achieve a >1 cm margin of normal tissue that is aimed for during traditional surgery. Critical structures such as cranial nerves and the carotid artery also preclude >1 cm margin typically, so the ideal margin to balance curative outcome and quality of life is to date unknown. During TORS, in an attempt to maximally preserve normal tissue, frequently the primary tumor is resected en bloc as the main specimen and intraoperative frozen section analyses are used to guide resection of additional margins. Hence, margin status can be difficult to determine after TORS given the uncertainty regarding the exact physical relationship between the main specimen resection surfaces and separately submitted additional margin samples. Further, pathologic assessment of margins is complicated. Factors such as tissue folding, mucosal shrinkage, and cautery artifact, make histopathologic assessment of margins difficult. Additionally, the orientation of the main resection specimen may be difficult to maintain once it is excised and the initial relationship between the resection surfaces of the main specimen and separately submitted additional margin samples may be unclear. However, this ambiguity could be clarified with the pathologist following a MDTB discussion with the operating surgeon.

Currently, there are no standardized criteria to determine margin status apart from a pathology report, and as to what constitutes a positive margin after TORS that warrants adjuvant chemotherapy. In the absence of validated standards, we classified main resection margin status as "clear", "positive" or "close" using consistent criteria. Separately submitted additional margins samples were used during multi-disciplinary correlation and discussion to determine the margin status that drove the decision to offer chemotherapy. Based on these definitions and the existing challenges with determining final margin status, we sought to (1) identify the frequency of discrepancies in margin status between the main resection specimen as assessed by pathologist versus multi-disciplinary team discussion; (2) how patterns of adjuvant chemotherapy are affected by margin status in the TORS setting; and (3) determine the recurrence rates based on the final margin status as determined by the multi-disciplinary tumor panel discussion.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

We performed an Institutional Review Board approved retrospective case series of all subjects who had undergone TORS using data from the University of Washington Medical Center from January 1, 2010 to December 31, 2015. De-identified and blinded patient information was then pooled for final analysis. All patients with head and neck squamous cell carcinoma (HNSCC) who underwent primary TORS management at our institution were included. We excluded those with recurrent disease, previous chemotherapy or radiation therapy to the head and neck region, unknown primary, non-oropharyngeal location of squamous cell carcinoma, and incomplete records. For survival outcomes, we excluded those with less than 6 months of follow-up data.

2.2 | Margin technique

At our institution, we first perform an en bloc resection of primary tumor ("main resection specimen"). At the time of resection, an effort is made to keep mucosal margins at least 1 cm, and at least 5 mm of deep margins throughout. The exception is the tonsillar fossa where the deep margin is the superior constrictor. Previously, we inked and examined the specimen with the pathology team and sectioned the specimen to determine high risk areas where further biopsies were warranted. However, as we gained experience, our practice has transitioned such that once excised, the main specimen is inspected by the surgical team to determine any high-risk areas intraoperatively without specimen sectioning. The specimen is inked intraoperatively and findings are discussed with the pathology team. Corresponding mucosal margins are obtained from the surgical bed for frozen section analysis, typically a four-quadrant mucosal margin assessment and at least two deep margins. Further margins are obtained from areas of concerns based on palpation of the specimen. All additional margins measured an average of 3–5 mm. If intraoperatively a margin was close or positive on the surgical specimen by gross inspection, then a wider re-resection was performed when possible and submitted as an additional permanent specimen. Exceptions to this included when a wider re-resection would denude the carotid artery along the tonsillar fossa or significantly infringe upon the soft palate superiorly; or if lesion extended to the hyoid bone for tongue base lesions or if re-resection would significantly cross the midline aspect of the tongue base necessitating bilateral lingual artery ligation. Ultimately, additional wide re-resections for close or suspiciously positive margins on gross examination of the specimen was based on surgeon's discretion with use of a buccopharyngeal flaps to provide carotid coverage or palatal reconstruction if deemed necessary, though the use of local reconstruction is rare in our practice. In the rare occasions when an intraoperative frozen section was called

"negative" but later changed to "positive" on further analysis or permanent main specimen was found to have a "positive" margin, patients were taken back for pathologic margin clearance.

2.3 | Main outcome measure assessment

Main resection margin status and the status of additional margins were determined from the pathology report. Given the uncertainties harbored by the pathologists regarding the precise location of additional margins with respect to a positive or close margin on the main specimen, our approach is for the pathologist to report separately on the en bloc specimen and additional margins and leave the final assessment of overall margin status that drives the decision to offer chemotherapy to the MDTB discussion. Three factors are critical to this retrospective correlation: (1) intraoperative inking of the surfaces of the main resection specimen by the surgeon to accurately and permanently identify all the different critical margin surfaces; (2) clear and unambiguous labeling of the separately submitted margin samples so their relation to the main resection specimen remains known; (3) standard synoptic pathologic reporting of margins that includes measured distances to critical surfaces.

Positive margins were defined as tumor present at the inked margin and/or <1 mm, clear margins were those with ≥3 mm of normal tissue from the tumor (ECOG 3311), and close margins were described as presence of tumor within 2 mm from the inked edge, with the exception noted above. Multi-disciplinary team discussion modified the margin status based on consideration of additional intraoperative margins and the following criteria of margins on the main specimen: "clear" if >2 mm, "close" if 1–2 mm; and "positive" defined as invasive carcinoma or carcinoma in situ within 1 mm from the edge of resection, and not superseded by additional tissue found to be free of histopathologic disease. For tonsillar carcinoma where the width of superior constrictors is in the millimeter range, the deep margin was dichotomized as either clear or positive.

2.4 | Data collection and statistical analysis

We used an Excel database and abstracted patient, tumor, and treatment characteristics including gender, age, location of the cancer, HPV (human papillomavirus) status, operative findings, pathology details including margin status and extracapsular spread, corrected margin status following a multi-disciplinary discussion between the surgeon and pathologist, receipt of adjuvant radiation with or without chemotherapy, if applicable, and follow up details from the available medical records. Local recurrence was defined as tumor recurrence within the surgical bed of the primary location. Regional recurrence was defined as tumor recurrence in the neck lymph nodes. Fisher's exact test was used to explore the relationships between margin status call and receipt of chemotherapy. A p-value of <.05 was deemed to indicate statistical significance.

TABLE 1 Selected characteristics of study participants.

Patient characteristics ($n = 57$)	
Age	
40–50	9
50–60	19
60–70	24
>70	5
Gender	
Male	50
Female	7
Smoking	
Current	2
Previous history	26
Never	29
HPV/p16 status	
Positive	50
Negative	0
Unknown	7

TABLE 2 Selected pathologic characteristics of study participants.

Pathologic patient characteristics ($n = 57$)	
Tumor stage	
T1	21
T2	30
T3	5
T4	1
Nodal stage	
N1	8
N2a	13
N2b	23
N2c	3
N3	3
Location	
Base of tongue	32
Tonsil	23
Both	2
Extracapsular spread	
Positive	15
Negative	41
Unknown	1
Post-operative adjuvant radiation therapy	
Yes	47
No	10
Post-operative adjuvant chemotherapy	
Yes	20
No	37

3 | RESULTS

3.1 | Patient and treatment characteristics

A total of 57 subjects met the eligibility criteria for the study. Selected patient characteristics are present in Table 1. The median age was 60 years old, ranging from 45 to 79. All subjects that were tested were HPV or p16 positive; of which, 2/50 (4.0%) were current smokers. Everyone was evaluated in our otolaryngology clinic with a comprehensive history and physical examination that included flexible fiberoptic laryngoscopy. Prior to their TORS operation, all had pathologic confirmation of squamous cell carcinoma from the head and neck.

Each surgery included examination under anesthesia with palpation, direct laryngoscopic evaluation of the upper aerodigestive tract, and TORS resection of the one or more of the following: base of tongue, palatine tonsil, and lateral pharynx. Management of cervical lymphadenectomy was variable. A majority (43/57, 75.4%) underwent a neck dissection on the same day. Twelve underwent staged surgery with a neck dissection either prior to their TORS procedure or after TORS. A neck dissection was deferred in 2/57 (3.5%) patients due to questionable resectability found at the time of TORS. Selected pathologic characteristics are presented in Table 2. Of the 41 without evidence of extracapsular spread on nodal pathology, 36/41 (87.8%) did not receive chemotherapy. Of note, five subjects underwent repeat resection with TORS to achieve clear margins. Table 3 shows the frequency of margins obtained and range of other margins. In general, we perform a standard four quadrant mucosal excision with additional margins for suspicious areas.

3.2 | Margin status calls

Based on the pathology assessment of the main specimen, margins were clear in 12/57 (21.0%), close in 16/57 (28.0%), and positive in 29/57 (50.8%). After multi-disciplinary discussion following the aforementioned criteria and consideration of additional margins, margin status was clear in 50/57 (87.7%), close in 5/57 (8.7%), and positive in 2/57 (3.5%) (Table 4). Of the 29 where the main resection specimen margin was positive per the pathology report, the cases were reclassified to 26 clear, 1 close, and 2 true positive following the multi-disciplinary discussion.

Surgical margin status is one of the key determinants to offer chemotherapy. When looking at all subjects, main specimen resection margin status was not associated with receipt of chemotherapy ($p = .08$), whereas final margin status determined by the multi-disciplinary team was ($p = .04$). When limiting to those without extracapsular nodal disease ($n = 41$), two had positive margins per multi-disciplinary team discussion, and both received chemotherapy. Although 19 (of 41) had positive main resection margins per the pathology report, only 4/19 (21.0%) of these cases received chemotherapy. For those without extracapsular spread, margin status call based on multi-disciplinary discussion was associated with receipt of chemotherapy ($p = .02$), whereas main resection margin status was not ($p = .41$) (Table 5). Among those without extracapsular spread and clear margins per multi-disciplinary discussion, three subjects received chemotherapy, all with N2b nodal disease. One subject was in a clinical trial whereas the other two were willing to receive additional treatment to possibly decrease their risk of recurrence.

3.3 | Patient outcomes

The median follow up time was 28.4 months. There were 26 subjects with positive main resection specimen margins and clear final margins per multi-disciplinary discussion; among this cohort, only two subjects developed a local recurrence. One received adjuvant chemotherapy

TABLE 3 Frequency of types of margins obtained.

Types of margins	Frequency
Four quadrant mucosal margins	45/57 (78.9%)
	Median (range)
Deep margins	1 (1–5)
Frozen margins	5 (1–10)
Total margins	6 (2–11)

TABLE 4 Variation in margin status calls.

	Multi-disciplinary discussion	Pathology report
Margin status		
Clear	50	12
Positive	2	29
Close	5	16

TABLE 5 Margin status and chemotherapy in subjects without extra-capsular spread.

	Received chemotherapy ($n = 5$)	No chemotherapy ($n = 36$)	
Main resection margin			$p = .41$
Status			
Clear	1	11	
Positive	4	15	
Close	0	10	
Final margin status per multi-disciplinary discussion			$p = .02$
Clear	3	34	
Positive	2	0	
Close	0	2	

prior to recurrence, whereas the other received it in a delayed manner due to initial non-compliance. There was another subject with clear main resection specimen margins and clear final margins per multi-disciplinary discussion who developed a regional recurrence. Thus, the overall recurrence rate was 3/53 (5.7%). All three had a base of tongue primaries with nodal disease at presentation, but no extranodal extension. One patient had a regional nodal recurrence and two had local recurrences in the primary tumor bed. Of the two with local recurrence, both were bases of tongue primaries. One had clear margins on both the pathology report and tumor board discussion, and also received postoperative radiation therapy. This patient recurred two times. The other case was reported as a positive margin on the pathology report, but considered to be a clear margin after multi-disciplinary discussion. This patient also received chemoradiation after the TORS procedure. The subject who developed a regional nodal recurrence was recommended to undergo post-operative radiation therapy but had declined. Neck recurrence was diagnosed 10 months after TORS, which was then managed with a neck dissection followed by delayed chemoradiation. Importantly, there were no recurrences from the instances ($n = 24$) where the pathology report was changed to "clear" by the TORS surgeon and no adjuvant therapy (neither chemo nor radiotherapy) was delivered.

It is possible that subjects who received adjuvant therapy outside of the University of Washington Medical Center with a positive margin status per pathology report were given chemotherapy despite absent extracapsular spread and clear margins after multi-disciplinary discussion. In our study, 4/57 (7.0%) had clear margins after multi-disciplinary discussion without pathologically proven extracapsular spread, but still received chemotherapy. Two of these subjects were in a clinical trial. One had carotid encasement with unresectable neck disease thus chemotherapy was added. The last had involvement of the level 4 neck nodes, which is associated with poorer prognosis; since this subject was young and otherwise healthy, chemotherapy was also given to help decrease the risk of recurrence.

4 | DISCUSSION

In this study, we sought to compare the differences in margin status call between the pathologists and the multi-disciplinary discussion, and how the decision to offer postoperative chemotherapy is affected by it. We found that the majority (27/29) subjects who were reported to have positive margins per the initial pathology report, were rendered to be clear margin status after a multi-disciplinary team discussion between the TORS surgeon and the pathologist. Receipt of chemotherapy correlated with the latter, but not with initial main specimen margins. Only two subjects recurred locally in the primary tumor bed (tongue base) and both had received chemotherapy. One of them was reported as clear margins by the initial pathology report and the other was reported as positive margin initially and deemed clear after the multi-disciplinary discussion. Thus, there was no detriment in converting a positive margin call by the pathologist to a clear margin status following a discussion with the TORS surgeon, and toxic chemotherapy could be avoided with this approach.

As stated previously, numerous factors affect margin status including tissue processing, cautery artifact, mucosal shrinkage, and pathologist interpretation. Although the surgeon may be obtaining what grossly appears to be an adequate cuff of tissue, fixation can induce shrinking of up to 30%, which can affect margin status interpretation.[6–9] Cautery artifact also affects the true margin status, as it results in peripheral coagulation that is 0.3–0.5 mm wide.[10,11] All this is further compounded when using minimally invasive approaches such as TORS, as it can be challenging to consistently obtain widely clear margins. Steiner et al. first described piecemeal resection during transoral endoscopic laryngeal cancer resections proving its feasibility and showing similar outcomes in survival when compared to en bloc resection.[12] This concept is often used with transoral surgical techniques, specifically for the resection of additional margins. Even after labeling the margins, it is challenging to determine exactly what part of the main specimen they correlate with. Through the help of the resecting surgeons' input some of the ambiguity is alleviated. Yet, there is always some potential for error inherent to this interpretation and no definitive guidelines exist. It is for this reason that at our institution, our pathologists report margin status based on the distance of the edge of the tumor to the cut edge of the main specimen and report additional margins separately. This leaves the final interpretation of the "true" margin to the treating providers with input from the TORS surgeon.

In a multi-institutional study by Weinstein et al. regarding TORS feasibility, this challenge is clearly exhibited as each of the participating institutions held different definitions as to what constituted a close margin.[13] Yet, it is based on these definitions that patients may receive adjuvant therapy confounding comparative evaluation of cancer specific outcomes. Furthermore, additional confusion can arise if medical and radiation oncologists are left to interpret the pathologist's reports without input from the TORS surgeon. This problem gets magnified when subjects undergo surgical resection at one institution, but receive adjuvant therapy at another.

Recommendations published by the National Cancer Institute in 2011 included "use of frozen section to guide resection until margins are tumor-free circumferentially around the tumor." Furthermore, close margin can be recorded, but should not influence the risk status of the tumor or subsequent treatment.[19] Despite these recommendations, close margins of the primary specimen are frequently used to dictate whether the primary tumor bed should be irradiated and to what extent. This may be especially true in subjects with aggressive tumor pathology or those who wish to reduce their risk of recurrence. In our study, after multi-disciplinary discussion, five subjects were deemed to have close margin; all received radiation therapy at doses between 60 and 65 Gy to the primary tumor bed, with chemotherapy reserved only for those with evidence of extracapsular spread on nodal pathology. Regardless of the cutoff utilized, determination of the post-operative adjuvant therapy requires a thorough evaluation of the tumor stage, general patient condition, and functional issues.[14]

Wong et al. looked at oral and oropharyngeal cancers to determine the influence of margin resection on local recurrence and disease specific survival noting that a cutoff of ≤1.6 mm had a significant

adverse association with both, and thus recommended a cutoff of 2 mm as a determinant on whether postoperative adjuvant therapy should be used.[15] In some settings however, a 2 mm margin may not be obtainable. In fact, many head and neck surgeons who perform TORS are aware of the inherent difficulty with obtaining a widely clear deep margin, particularly for cancers originating in the palatine tonsils where the superior constrictor is barely a few millimeters thick. There is often penetration or invasion of the superior constrictor muscle even with early stage (T1 or T2) cancers, which are those commonly treated by TORS.[16] The parapharyngeal fat and the styloglossus and stylopharyngeus muscles exist deeper to the superior constrictor musculature. They are not true barriers to the spread of cancer and are therefore not useful in considering the margin status. Thus, deep margins for the tonsil are often considered close by default.[4] Park et al. concluded that anything beyond T2 tumor stage or N1 nodal disease (AJCC7) should automatically warrant multimodality therapy.[16] Similarly, only patients with T1–T2, N0–N1 (AJCC7) cancers in our cohort underwent surgery alone, avoiding adjuvant therapy. We dichotomized the margin status of the deep of the tonsil as either positive or negative based on the superior constrictor status. Additional margins of the parapharyngeal space were obtained only to confirm negativity. Treating the deep margin of the tonsil in this fashion did not lead to any recurrences thus far in a median follow up time of 28.4 months.

Hamzany et al. reviewed the assessment of margin status for transoral laser and robotic surgery noting that controversies exist regarding assessment and interpretation of the margins. They noted several conflicting studies in both glottis and non-glottic sites, and accurately concluded that any adjuvant treatment decision should include the surgeon's interpretation with regards to completeness of resection.[17] This is in accordance with our study, which shows that receipt of chemotherapy was associated with margin status determination based on the multi-disciplinary discussion, but not with margin status as dictated by the pathology report.

How best to account for additional intraoperative margins also remains a dilemma. Kerawala and Ong asked surgeons to identify proposed sampling in 14 cases, and asked to relocate them after 5 min; they noted a mean error of 9 mm for mucosal sites, and 12 mm for deep sites, with error exceeding 1 cm in close to 1/3 of cases.[18] This begs the question of how accurate any re-resections or additional margins are. To help overcome this challenge, Hinni et al. recommended a technique called "margin mapping," which represents one potential solution to allow for close correlation of any additional margins obtained.[4]

A survey conducted through the American Head & Neck Society concluded that there are no uniform criteria to define a clear surgical margin. There was also an added level of complexity about how to define a margin that contains carcinoma—in situ or dysplasia.[19] Regardless of the technique utilized, both head and neck surgeons and pathologists agree that a consistent, and widely accepted system with multi-disciplinary communication is crucial to begin answering these questions regarding margin status and its influence on adjuvant treatment and overall prognosis.[4,9,14,17]

Of note, all subjects that were tested had p16 positive tumors. It is possible then that the low rate of recurrence is not necessarily due to a better margin interpretation by the TORS surgeon, but a function of better response to adjuvant radiotherapy accounted for this despite it lacking chemotherapy. 50.9% of these p16 positive patients were, current or previous smokers. Of the three recurrences, two patients were never smokers and one was a present smoker. Thus, in this study, the sample size makes it difficult to draw any definitive conclusions between smokers and non-smokers. None of the patients exhibited HPV-negative tumors. Results of this study may have more limited applicability in HPV negative cancers.

Limitations of this study include its retrospective nature and limited sample size. Reporting of margin status may be variable among pathologists making it difficult to generalize this study to other institutions until there is consensus about the best approach. Additionally, we used chemotherapy as one surrogate marker for action based on margin status. This can be problematic as the final recommendation of postoperative adjuvant chemotherapy is not based solely on margin status or extracapsular spread. Additional factors such as performance status and social factors are all taken into account. For our study, three subjects had positive margins based on multi-disciplinary discussion, and all received postoperative chemotherapy.

5 | CONCLUSION

Surgical management with TORS frequently results in discrepancy between the margin status of the main resection specimen and final margin status as adjudicated by the multi-disciplinary team. Our experience clearly shows that careful determination of true margin status reduces unnecessary chemotherapy, without increasing the risk of local recurrence. It is imperative that the TORS surgeon become involved in margin interpretation and that there is a clear and consistent working relationship with the pathology team on how to optimally identify, track and correlate margins in this region of difficult anatomy.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest to disclose.

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