Robotic Surgery for Primary Head and Neck Squamous Cell Carcinoma of Unknown Site

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IMPORTANCE Identification of the primary site in head and neck squamous cell carcinoma (HNSCC) is crucial because it improves the patient’s prognosis and minimizes morbidity from treatment.

OBJECTIVES To determine the efficacy of transoral robotic surgery (TORS) in identifying unknown primary sites of head and neck squamous cell carcinoma.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, multi-institutional case series from January 1, 2010, to February 28, 2013, in which data were pooled from the following 6 institutions: University of Washington Medical Center, The University of Texas MD Anderson Cancer Center, University of Alabama–Birmingham Hospital, The University of Texas Medical School at Houston, Johns Hopkins Hospital, and Oregon Health Sciences University. All patients diagnosed as having HNSCC of an unknown primary site who underwent TORS to identify the primary site were included in the study. We excluded those with recurrent disease, a history of radiation therapy to the head and neck, or evidence of a primary tumor site based on previous biopsy results.

MAIN OUTCOME AND MEASURE Identification of the primary tumor site.

RESULTS Forty-seven patients were eligible for the study. The tumor site was identified by TORS in 34 of 47 patients (72.3%). The primary site was located in the base of tongue for 20 patients (58.8%) and the palatine tonsil for 13 patients (38.2%), with 1 patient having a primary site in both the base of tongue and the palatine tonsil. Suspicious physical examination findings were present in 23 of 47 patients (48.9%), with positive and negative predictive values of 56.5% and 25.0%, respectively. Of those who underwent any imaging, 16 patients had suspicious findings, with positive and negative predictive values of 50.0% and 16.7%, respectively. In 18 of 47 patients (38.3%), both preoperative radiographic and physical examination failed to suggest a primary site. Of these 18 patients, 13 (72.2%) were identified after undergoing TORS.

CONCLUSIONS AND RELEVANCE We demonstrate that TORS is a useful approach to identify and treat the primary site in patients with HNSCC who present with an unknown primary site.
ead and neck squamous cell carcinoma (HNSCC) often presents as a neck mass, and in more than 90% of cases, a primary site can be identified. The remaining 10% are defined as having an unknown primary tumor, most of which are squamous cell carcinomas. When the primary tumor is localized, the most common sites are the palatine and lingual tonsils. Identification of the primary site is crucial because it improves the patient's prognosis and minimizes morbidity from treatment because such patients often require extended-field radiotherapy to cover all of the Waldeyer ring.

No standard algorithm exists for the workup of an unknown primary metastatic tumor. Traditionally, the workup requires a combination of history, physical examination, radiologic imaging, and further endoscopic evaluation with the patient under general anesthesia. The use of positron emission tomography (PET) remains controversial. Identification of the primary site ranges from 21% to 52%. Further evaluation with direct laryngoscopy (with or without esophagoscopy or bronchoscopy) with the patient under general anesthesia is often required to achieve better visualization and palpation of the mucosal surfaces of the upper aerodigestive tract and to obtain indicated biopsy specimens for the diagnosis of malignant neoplasms at a particular site. Despite this, in a series by Pattani and colleagues, 43% of cases of an unknown primary tumor were not identified after panendoscopic evaluation.

The emergence of techniques in transoral endoscopic head and neck surgery and its more widespread use may help to identify those tumors that were previously unknown. The use of a surgical microscope or a rigid endoscope provides the surgeon with better visualization of critical anatomy within the laryngopharynx, especially the Waldeyer ring. With this improved visualization, it is reasonable to expect that head and neck surgeons can more frequently identify the unknown primary site in HNSCC. A recent study found that examination under anesthesia (EUA) coupled with transoral laser microsurgery (TLM) identified the primary site in 94% of patients with unknown primary metastatic carcinomas to the neck compared with only 25% with EUA alone. Because most primary tumors in this study represented early T1 tumors, with 19 of the 20 localized to the oropharynx, the results highlight the importance of methods that allow for a magnified and thorough inspection of tonsillar tissue where primary tumors can hide. In addition, the ability to perform a radical tonsillectomy or a composite submucosal resection of the tongue base can help in diagnosing and offering definitive therapy to the primary site.

In ways similar to TLM, the use of transoral robotic surgery (TORS) has the potential to offer both improved visualization and definitive treatment of the primary site. However, differences in tissue evaluation and resection are likely to exist between these techniques. In addition, the use of TORS to aid in the identification and treatment of the unknown primary tumor has not been clearly established. In this study, we report a multi-institutional experience using EUA with TORS as part of the workup of the unknown primary site in patients with metastatic carcinoma to the neck nodes. The goal of our study was to determine the efficacy of TORS in localizing the primary site of the malignant tumor for regional metastatic HNSCC. Our secondary goal was to describe the surgical management of the diagnosed primary tumor after TORS.

Methods

Study Design and Participants
We performed a retrospective case series review using pooled data from the following 6 institutions: University of Washington Medical Center, The University of Texas MD Anderson Cancer Center, University of Alabama–Birmingham Hospital, The University of Texas Medical School at Houston, Johns Hopkins Hospital, and Oregon Health Sciences University. The institutional review board of each participating institution approved a retrospective review of all patients who had undergone TORS from January 1, 2010, to February 28, 2013. Some institutions had obtained a waiver of consent for retrospective data analysis, and some had received consent from patients a priori. Deidentified, masked patient information was then pooled for final analysis. All patients diagnosed as having HNSCC with an unknown primary site despite a physical examination and/or preoperative radiograph(s) who underwent directed biopsies with TORS to aid in the workup of the primary site were included. We excluded those with recurrent disease, previous radiation therapy to the head and neck region, and/or previous biopsy specimens suggestive of the primary tumor site.

Evaluation and Imaging Assessment
Evidence suggestive of the primary tumor site was based on clinical and/or radiographic evaluation. Clinical evaluation included a thorough head and neck physical examination with a flexible fiberoptic scope examination. Radiographic imaging included ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and PET. For each case included, the lack of a definitive diagnosis of the primary tumor site prompted further operative evaluation with TORS. Each operative procedure was preceded with a direct laryngoscopy by the surgeon performing TORS.

Data Collection and Statistical Analysis
Each institution was provided a standard database for abstraction of clinical outcomes data, including preoperative radiographic and physical examination findings and surgical and pathologic details. The Fisher exact test was used to explore the relationships of age and sex on initial nodal stage. The detection rate for an HNSCC of an unknown primary site using TORS was calculated, and the effect of the procedure on staging was analyzed descriptively.

Results
Forty-seven patients met the study criteria for an unknown primary tumor. Selected characteristics are presented in Table 1. The mean age of the patients was 57.3 years (range, 40-78 years). All patients with an unknown primary tumor presented with a neck mass, yet there was a wide distribution in the size of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57.3 years (range, 40-78 years)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male: 25, Female: 22</td>
</tr>
<tr>
<td><strong>Unknown Primary Site</strong></td>
<td>Head and neck: 23, Lung: 14, Other: 10</td>
</tr>
<tr>
<td><strong>EUA with TORS</strong></td>
<td>Yes: 47, No: 0</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Squamous cell carcinoma: 43, Adenocarcinoma: 4</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>T1: 20, T2: 27</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>Median: 24 months, Range: 6-108 months</td>
</tr>
</tbody>
</table>
the nodal tumor. Most had unilateral lymphadenopathy with nodal tumors of less than 6 cm. No association was found among sex, age, or human papillomavirus status and level of neck nodal disease ($P = .15$, $P = .57$, and $P = .85$, respectively). Of those tested, slightly more than three-fourths were human papillomavirus or p16 positive, yet in 27.6% this testing was not performed.

The imaging workup performed at each institution was highly variable and is documented in Table 2. Contrast-enhanced CT was the most common modality obtained in 38 of the 47 patients (80.8%), whereas 27 of 47 (57.4%) underwent combination PET and CT. The least common modalities were ultrasonography and MRI. Less than 15% of the study participants had no available imaging results before their TORS operation. Eight of the 38 (21.0%) had suspicious findings on their diagnostic CT scan, whereas 11 of 27 (40.7%) had suspicious findings on their PET-CT scan. Within the former group, 4 also had suspicious findings and supporting evidence of cancer on PET-CT, 2 had unremarkable PET scans, and 2 did not undergo PET-CT. For the remaining 7 of the 11 patients with suspicious PET-CT findings, 6 (85.7%) had an unremarkable diagnostic CT scan, whereas the remaining patient did not undergo this type of study. In summary, of those with imaging results, 16 of 40 patients (40.0%) had suggestive findings on contrast-enhanced CT, MRI, PET-CT, ultrasonography, or multiple techniques, with positive and negative predictive values of 50.0% and 16.7%, respectively.

Table 3 lists the detection rates based on findings of preoperative workup. For the 4 cases with suspicious findings in both modalities (contrast-enhanced CT and PET-CT), 2 were accurately identified, whereas 2 remained unknown. In the 6 cases with suspicious PET-CT findings without supporting CT evidence, the unknown primary site was accurately identified in 4 of 6 (66.7%). Two cases had suspicious findings based on CT only, for which one remained unknown and the other was identified in a different site than what the imaging suggested. Altogether, 8 patients had notable findings for one imaging modality, whereas the other remained unremarkable. In these cases, PET-CT fared better at identifying the primary site (4 of 8 [50.0%]), with 2 false-positive cases compared with a diagnostic CT that failed to identify any primary tumors.

Physical examination findings were suspicious in 23 of 47 patients (48.9%). Of these, 10 had suspicious findings on imaging, but in 3 of 10 (30.0%) the physical examination findings did not coincide with the imaging results. One patient presented with a right N2c neck mass. This patient had undergone multiple right-sided directed biopsies, including an ipsilateral tonsillectomy, with imaging suggestive of a left tonsillar primary tumor and physical examination revealing lingual tonsillar hypertrophy. This patient underwent a left tonsillectomy and bilateral base of tongue resection, but the primary tumor was not identified. Another patient had a previous, unremarkable left tonsil biopsy specimen, with imaging suggestive of a supraglottic primary tumor and physical examination findings sug-

| Table 1. Selected Characteristics of Study Participants by Institution |
|-----------------|-------|------|------|-------|------|------|------|
| Characteristic   | UWMC | UAB | MD Anderson | UT-Houston | Hopkins | OHSU | Total |
| Age, y           |
| 40-50            | 4    | 0   | 0    | 2     | 2     | 1    | 9    |
| 51-60            | 9    | 4   | 1    | 2     | 3     | 1    | 20   |
| 61-70            | 5    | 2   | 1    | 2     | 3     | 1    | 14   |
| >70              | 1    | 1   | 1    | 0     | 1     | 0    | 4    |
| Sex              |
| Male             | 18   | 6   | 3    | 5     | 8     | 2    | 42   |
| Female           | 1    | 1   | 0    | 1     | 1     | 1    | 5    |
| HPV or p16       |
| Yes              | 10   | 4   | 2    | 0     | 7     | 3    | 26   |
| No               | 1    | 1   | 1    | 4     | 1     | 0    | 8    |
| Unknown          | 8    | 2   | 0    | 2     | 1     | 0    | 13   |
| Tumor stage      |
| Tx               | 7    | 3   | 0    | 0     | 3     | 0    | 13   |
| T1               | 10   | 3   | 3    | 6     | 6     | 3    | 31   |
| T2               | 2    | 1   | 0    | 0     | 0     | 0    | 3    |
| Nodal stage      |
| N1               | 2    | 3   | 1    | 3     | 1     | 1    | 11   |
| N2a              | 2    | 2   | 0    | 1     | 3     | 1    | 9    |
| N2b              | 10   | 1   | 2    | 2     | 4     | 1    | 20   |
| N2c              | 3    | 0   | 0    | 0     | 1     | 0    | 4    |
| N3               | 2    | 1   | 0    | 0     | 0     | 0    | 3    |

Abbreviations: HPV, human papillomavirus; OHSU, Oregon Health Sciences University; UAB, University of Alabama–Birmingham Hospital; UT-Houston, The University of Texas at Houston; UWMC, University of Washington Medical Center.

* $P$ value represents the association between a specific category and the preoperative nodal stage.
gestive of a palatine tonsil tumor, yet again no primary tumor was found. In yet another patient, the primary tumor was located in the left tonsil, which had suspicious uptake on PET-CT, but physical examination findings were concerning for a base of tongue lesion. For physical examination, the false-positive rate was 43.4%, and the positive and negative predictive values were 56.5% and 25.0%, respectively. When considering all pre-TORS workup, including physical examination, fiberoptic endoscopy, and imaging, 15 of 47 (31.9%) had no findings suggestive of a primary tumor site.

Eighteen of 47 patients (38.3%) underwent a biopsy of the upper aerodigestive tract at an outside hospital for workup of their unknown primary tumor before undergoing TORS. Most of these biopsies were obtained from the oropharynx, usually involving a tonsillectomy (6 of 18 [33.3%]) or biopsy of the tonsil (7 of 18 [38.9%]) and/or base of tongue biopsy (14 of 18 [77.8%]). Ten of 18 underwent biopsies of both the base of tongue and the palatine tonsil. After TORS, the primary site was identified in 11 of 18 patients (61.1%) who underwent previous biopsies.

Details regarding operative and pathologic findings after TORS are presented in Table 4. Operative management was limited to base of tongue excision or tonsillectomy, but variability occurred in whether resection was unilateral, bilateral, or in conjunction with a tonsillectomy. The extent of the resection of the base of tongue ranged from a submucous resection of the lingual tonsils to a unilateral, partial glossectomy in patients in whom the primary tumor was identified intraoperatively. Most patients (41 of 47 [87.2%]) underwent a base of tongue resection, with less than half undergoing a unilateral excision (17 of 41 [41%]). Similarly, tonsil resection ranged from a bilateral tonsillectomy to a radical tonsillectomy. Twenty-seven of the 47 also underwent a tonsillectomy, 6 of which underwent a tonsillectomy alone. Of these 27 patients who underwent tonsillectomy, slightly less than one-third had a radical tonsillectomy. Thirteen patients underwent an ipsilateral tonsillectomy, and 17 underwent an ipsilateral isolated base of tongue resection, with 10 in each group (76.9% and 58.8%, respectively) having suspicious preoperative workup findings.

Cervical lymphadenectomy was also highly variable. Eight patients did not undergo a neck dissection. Six underwent treatment of neck nodal disease before TORS, with 2 undergoing only an excisional biopsy. Of the remaining 33, 24 underwent same-day surgery, 8 underwent a neck dissection as a second stage procedure, and 1 had it after radiation therapy. For 34 of 47 patients (72.3%), a primary site was successfully identified, with most localized to the base of tongue (n = 20); the remaining were identified in the palatine tonsil (n = 13), and 1 patient with 2 synchronous primary tumors, in the base of tongue and the palatine tonsil. The size of the primary site ranged from 0.3 to 3.0 cm, with a mean of 1.2 cm. Surgical treatment, whether a tonsillectomy or partial glossectomy with or without a partial pharyngectomy, was used for diagnosis and management because margin status for all identified primary tumors was clear in 29 of 34 patients (85.2%). In this group, 2 underwent repeat excision to achieve full clearance, and another 2 had close margins, within 1 mm. For the remaining 5 with positive margins, all were recommended to receive or received adjuvant radiotherapy.

Twenty-one patients had no suspicious findings on physical examination and radiographic imaging, if performed, or had conflicting information between the two. In this group, 16 of 21 patients (76.2%) were successfully identified. Three of these patients did not undergo any radiographic imaging before TORS, leaving a total of 18 patients who had a complete workup, including physical examination and preoperative imaging, without any suspicious findings or had contradictory workup results between the two. Selected characteristics for this group are given in Table 5. The nodal stage at presentation was N1.

Table 2. Preoperative Workup by Institution

<table>
<thead>
<tr>
<th>Workup</th>
<th>UWMC</th>
<th>UAB</th>
<th>MD Anderson</th>
<th>UT-Houston</th>
<th>Hopkins</th>
<th>OHSU</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>17/19</td>
<td>1/7</td>
<td>3/3</td>
<td>6/6</td>
<td>8/9</td>
<td>3/3</td>
<td>38/47</td>
</tr>
<tr>
<td>MRI</td>
<td>1/19</td>
<td>0/7</td>
<td>0/3</td>
<td>0/6</td>
<td>2/9</td>
<td>0/3</td>
<td>3/47</td>
</tr>
<tr>
<td>PET</td>
<td>10/19</td>
<td>1/7</td>
<td>1/3</td>
<td>6/6</td>
<td>7/9</td>
<td>2/3</td>
<td>27/47</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>4/19</td>
<td>1/7</td>
<td>0/3</td>
<td>0/6</td>
<td>1/9b</td>
<td>0/3</td>
<td>6/47</td>
</tr>
<tr>
<td>Physical examination</td>
<td>9/19</td>
<td>4/7</td>
<td>2/3</td>
<td>1/6</td>
<td>5/9</td>
<td>2/3</td>
<td>23/47</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; OHSU, Oregon Health Sciences University; PET, positron emission tomography; UAB, University of Alabama–Birmingham Hospital; UT-Houston, The University of Texas at Houston; WMC, University of Washington Medical Center.

* Imaging indicates how many patients underwent a specific study per institution.

b One patient underwent transoral ultrasonography.

f Physical examination findings refer to frequency of suspicious findings on physical examination per institution.

c Previous biopsy indicates site-specific breakdown of how many patients had undergone biopsies before presenting to the specific institution. Some patients underwent biopsies of multiple sites.
Despite the variety of options available, there continues to be advances in identifying an unknown primary tumor. During the past 7 decades, few changes and advances have occurred in identifying an unknown primary tumor. Most of all, previous studies have reported that identification of the occult tumor results in increased survival rates from 16% to 50% when not found compared with up to 58% to 100% if localized. In this study, we aimed to assess the efficacy of TORS in localizing the primary site of malignant neoplasms for regional metastatic HNSCC and to describe the surgical management of the diagnosed primary tumor after TORS. The primary site of the malignant neoplasm was identified in most patients even when limiting to those with unremarkable preoperative workup findings. Use of TORS allowed for diagnosis of the primary tumor site and definitive surgical treatment, usually in one setting.

Workup and management begin with a focused history and physical examination in addition to flexible laryngoscopy, but the criterion standard of diagnosis has been endoscopic visualization of the upper aerodigestive tract with the patient under general anesthesia, as suggested by Martin and Morfit in the mid-1940s. During the past 7 decades, few changes and advances have occurred in identifying an unknown primary tumor. Now, with more enabling and ubiquitous technologies, many patients can undergo some form of contrast-enhanced imaging and combination PET-CT. Operative evaluation with the patient under anesthesia is not limited to panendoscopy and biopsies; tools such as TLM and TORS are now available as well. Despite the variety of options available, there continues to be no set standard in the workup, diagnosis, and management of an unknown primary tumor of the head and neck region. In this study, we included all patients diagnosed as having an unknown primary HNSCC despite a physical examination and/or preoperative radiograph(s) and who underwent directed biopsies with TORS to aid in the workup of the primary site. We purposely did not exclude patients with suspicious findings on physical examination or imaging to illustrate the heterogeneity in the definition of an HNSCC with an unknown primary site among different institutions, to determine the predictive accuracy of the physical examination and imaging studies in diagnosing the primary site, and to evaluate how imaging results affect intraoperative decision-making. Significant variety was found in the management of an unknown primary tumor, specifically regarding the type of operation performed, the inclusion of the base of tongue and the tonsil, and the laterality. For our series, the primary tumor site was identified on the same side as the presenting neck mass. However, previous reports have addressed the possibility of bilateral or contralateral palatine tonsil disease. The incidence of the former was noted in 11.1% of primary tumors identified, whereas contralateral disease has been appreciated in up to 10% of patients. This, in addition to the resulting asymmetry of the remaining tonsil, argues for bilateral excision.

In our database of 47 patients, 34 primary tumor sites (72.3%) were identified, but more than half of the initial group had suspicious findings based on their preoperative workup, leaving a total of 18 patients with no suspicious findings based on physical examination, radiologic imaging, and previous workup or workup that led to contradictory information. Within this group, 72.2% were accurately identified. In a similar manner, Cianchetti et al retrospectively assessed the diagnostic workup (including CT, MRI, and PET) of an unknown primary tumor in the setting of squamous cell carcinoma metastatic to the cervical lymph nodes where panendoscopy with directed biopsies and a unilateral or bilateral tonsillectomy if indicated was used to diagnose the primary tumor. In a 20-year period, they noted a diagnostic rate of 53.4% in 236 patients, but when limiting it to only those with no physical examination or radiographic findings, the rate decreased to 29.2% for 72 patients. A comparable study noted an overall detection rate of 43% in 130 patients when using
### Table 4. Postoperative Pathologic Findings After TORS

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Final Stage Size</th>
<th>Site</th>
<th>TORS</th>
<th>Neck Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/54 TNX2b NA NA</td>
<td>Bilateral tonsillectomy, bilateral BOT excision</td>
<td>Second stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/M/58 T1N2a NA LBOT</td>
<td>Left BOT excision</td>
<td>Second stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/M/58 TXN2c NA LA</td>
<td>L tonsillectomy, bilateral BOT excision</td>
<td>After XRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/M/62 T1N1 1 cm L tonsil</td>
<td>L radical tonsillectomy, R tonsillectomy</td>
<td>Partial, before TORS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/M/67 T1N2b 2 cm LBOT</td>
<td>L BOT excision with lateral pharyngectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/M/62 TXN2b NA NA</td>
<td>Bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/M/46 T1N1 0.5 cm R tonsil</td>
<td>Bilateral BOT excision, L tonsillectomy, R radical tonsillectomy</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/M/71 T1N2b 0.9 cm LBOT</td>
<td>L BOT excision</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/M/60 T1N2b 1.5 cm Vallecula (BOT)</td>
<td>R BOT excision with lateral pharyngectomy</td>
<td>Second stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/M/55 T1N1 1.8 cm R tonsil</td>
<td>Bilateral tonsillectomy, biopsy of L GT sulcus, R lateral pharyngectomy</td>
<td>Second stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/M/56 TXN3 NA NA</td>
<td>Bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/M/63 TXN3 NA NA</td>
<td>Bilateral BOT excision</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/M/51 T1N2b 2.0 cm R tonsil</td>
<td>R radical tonsillectomy</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/M/56 TXN2b NA NA</td>
<td>Bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/M/53 T1N2a 2.0 cm R BOT</td>
<td>R BOT excision</td>
<td>Second stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/M/78 T2N2a 2.8 cm LBOT</td>
<td>L BOT excision, L tonsillectomy</td>
<td>Second stage</td>
<td></td>
<td></td>
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<tr>
<td>17/M/53 T1N2b 0.5 cm LBOT</td>
<td>L BOT excision, L tonsillectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/M/66 TXN1 NA NA</td>
<td>Bilateral tonsillectomy</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19/F/56 TXN1 NA NA</td>
<td>R tonsillectomy, R BOT excision</td>
<td>Second stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/M/64 TXN1 NA NA</td>
<td>Bilateral tonsillectomy, excision of R BOT</td>
<td>Before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21/M/50 T1N3 0.5 cm LBOT</td>
<td>L tonsillectomy, L BOT excision</td>
<td>Before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22/F/58 T1N2a 1.0 cm R tonsil</td>
<td>R radical tonsillectomy, L tonsillectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23/M/46 T1N2b 1.3 cm L tonsil</td>
<td>L radical tonsillectomy, L BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/F/51 T1N1 1.5 cm L tonsil</td>
<td>L radical tonsillectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25/M/65 T1N2b 1.3 cm R BOT</td>
<td>R radical tonsillectomy, bilateral BOT excision</td>
<td>Partial before TORS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26/M/52 T1N1 2.0 cm R BOT</td>
<td>Bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27/M/69 T1N1 0.6 cm R BOT</td>
<td>Bilateral tonsillectomy, bilateral BOT excision, partial epiglottectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/M/49 T1N2a 3 Foci, 0.2 cm each LBOT</td>
<td>L radical tonsillectomy, bilateral BOT excision</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/M/60 T2N2b 3.0 cm L tonsil</td>
<td>L radical tonsillectomy, L BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30/M/72 TXN2b NA NA</td>
<td>Bilateral BOT excision</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31/M/61 T1N2a 0.8 cm L BOT</td>
<td>Bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32/M/61 TXN2c NA NA</td>
<td>Bilateral tonsillectomy, bilateral BOT excision</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33/M/56 T1N2a 0.8 cm LBOT</td>
<td>L tonsillectomy, L BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34/F/48 T1N2a 0.3 cm LBOT</td>
<td>Bilateral BOT excision</td>
<td>Yes before TORS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35/M/57 TXN1 NA NA</td>
<td>Bilateral BOT excision</td>
<td>Yes before TORS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36/M/72 T1N2b 1 cm L tonsil</td>
<td>Bilateral tonsillectomy, L BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37/M/54 T1N2a 1.5 cm L GT sulcus (tonsil)</td>
<td>L BOT excision with lateral pharyngectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38/F/61 T1N2b 0.5 cm L tonsil</td>
<td>L partial pharyngectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39/M/49 T1N1 0.6 cm LBOT</td>
<td>L BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40/M/47 T1N2b 0.4 cm R BOT</td>
<td>Bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
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<tr>
<td>41/M/47 TXN2b NA NA</td>
<td>Bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42/M/44 T1N2b 0.3 cm L tonsil</td>
<td>Bilateral tonsillectomy, bilateral BOT excision, L partial pharyngectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43/M/53 TXN2c 0.8 cm L tonsil</td>
<td>L radical tonsillectomy, R tonsillectomy, bilateral BOT excision</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44/M/57 T2N2c 3 cm, 2.2 cm LBOT, L tonsil, 2 separate foci</td>
<td>Bilateral tonsillectomy, bilateral BOT excision, L partial pharyngectomy</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45/M/63 T1N2b 0.2 cm, 0.3 cm LBOT, 2 separate foci</td>
<td>Bilateral tonsillectomy, bilateral BOT</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46/M/56 T1N2b 0.7 cm LBOT</td>
<td>Bilateral BOT</td>
<td>Same day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47/M/48 T1N2b 0.5 cm LBOT</td>
<td>Bilateral BOT</td>
<td>Second stage</td>
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</table>

Abbreviations: BOT, base of tongue; GT, glossotonsillar; L, left; NA, not applicable; R, right; TORS, transoral robotic surgery; XRT, radiation therapy.
preoperative workup and panendoscopy, but again this number was greatly reduced (7 of 42 [17%]) when limiting the sample to those who had unremarkable physical examination and negative radiographic findings. More recently, Patnani et al13 looked at the utility of panendoscopy in a smaller sample size of 23 patients and noted that panendoscopy was able to identify the primary site in 57%. Their population included those with suspicious findings on PET-CT examination, which represented all but 1 of the identified primary tumors. Thus, when comparing our study’s identification rates to published series that used panendoscopy, TORS management was superior in identifying the primary site, with a rate of 72.3% of all patients and 72.2% of those without physical examination and/or radiographic findings or contradictory information between the two. In contrast to panendoscopy, the individual and overall detection rates noted in TORS (50% to 80%, depending on presence of physical examination and/or radiographic findings) were much higher, suggesting that regardless of the preoperative findings, TORS had a consistently higher diagnostic rate.2-13,24 This finding held true for our subset analysis, which was limited to those with unremarkable or contradictory preoperative workup findings.

Our study, however, reported a detection rate of TORS to be much lower than what was reported by Karni et al15 when using a TLM approach (17 of 18 [94.4%]). They also noted a rate of 3 of 12 (25.0%) for those who underwent a standard EUA. Although their exclusion criteria were similar to ours, PET-CT was not included for the diagnostic workup of an unknown primary tumor. One study26 noted success with the use of PET-CT with identification rates of 30 of 78 (38%) after physical examination and imaging had failed. Furthermore, multiple studies22-25 have suggested an increased rate of detection of up to 54% when PET-CT was used. Our study supports the use of combination PET-CT; in cases when there is conflicting information between contrast-enhanced CT and PET-CT, the latter fared better in identifying the primary tumor site.

Only one other study28 has examined the use of TORS in diagnosis and management of an unknown primary tumor. The authors reported an identification rate of 90% when performing a base of tongue resection using TORS. Their study, however, was limited by a small sample size of 10 patients, all of whom had previously undergone a laryngoscopy with examination while under anesthesia, which included random biopsies of base of tongue and pharynx and a tonsillectomy before TORS. Furthermore, in this group, the preoperative workup had failed to identify a primary site, yet 4 of 10 had suspicious findings on PET-CT. Most of the tumors were positive for human papillomavirus, raising suspicion of an oropharyngeal source when a tonsillar primary tumor has already been ruled out because all had undergone a previous tonsillectomy. Despite having had a previous base of tongue biopsy, a malignant tumor was not identified until a base of tongue re-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>PE Findings</th>
<th>Imaging Findings</th>
<th>Panendoscopy and Biopsy</th>
<th>Nod Stage</th>
<th>TORS</th>
<th>Tumor Stage</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>L N2b</td>
<td>Bilateral tonsillectomy, bilateral BOT excision</td>
<td>TX</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Enlarged BOT</td>
<td>PT asymmetry (L&gt;R)</td>
<td>Yes</td>
<td>L and R N2c</td>
<td>L tonsillectomy, bilateral BOT excision</td>
<td>TX</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>L N1</td>
<td>L radical tonsillectomy, R tonsillectomy</td>
<td>T1: 1 cm</td>
<td>L tonsil</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>L N2b</td>
<td>Bilateral BOT excision</td>
<td>TX</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Enlarged BOT</td>
<td>PT asymmetry (L&gt;R)</td>
<td>Yes</td>
<td>L N1</td>
<td>Bilateral BOT excision, L tonsillectomy, R radical tonsillectomy</td>
<td>T1: 0.5 cm</td>
<td>L tonsil</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>R N2b</td>
<td>R BOT excision with lateral pharyngectomy</td>
<td>T1: 1.5 cm</td>
<td>R vallecula (BOT)</td>
</tr>
<tr>
<td>7</td>
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<td>None</td>
<td>No</td>
<td>L N3</td>
<td>L tonsillectomy, L BOT excision</td>
<td>T1</td>
<td>L BOT</td>
</tr>
<tr>
<td>8</td>
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<td>None</td>
<td>No</td>
<td>R N2b</td>
<td>R radical tonsillectomy, R BOT excision</td>
<td>T1: 1.3 cm</td>
<td>R BOT</td>
</tr>
<tr>
<td>9</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>R N1</td>
<td>R tonsillectomy, R BOT excision, partial epiglottectomy</td>
<td>T1: 0.6 cm</td>
<td>R BOT</td>
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<tr>
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<td>None</td>
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<td>No</td>
<td>L N2a</td>
<td>Bilateral BOT excision</td>
<td>T1: 0.8 cm</td>
<td>L BOT</td>
</tr>
<tr>
<td>11</td>
<td>L PT swelling</td>
<td>Increased uptake</td>
<td>No</td>
<td>L and R N2c</td>
<td>Bilateral tonsillectomy, bilateral BOT excision</td>
<td>Tx</td>
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<tr>
<td>12</td>
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<td>None</td>
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<td>Bilateral BOT excision</td>
<td>T1: 0.3 cm</td>
<td>L BOT</td>
</tr>
<tr>
<td>13</td>
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<td>None</td>
<td>No</td>
<td>L N2b</td>
<td>Bilateral tonsillectomy, L BOT excision</td>
<td>T1: 1 cm</td>
<td>L tonsil</td>
</tr>
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<td>14</td>
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<td>None</td>
<td>No</td>
<td>L N2a</td>
<td>L BOT excision with lateral pharyngectomy</td>
<td>T1: 1.5 cm</td>
<td>L GT sulcus (tonsil)</td>
</tr>
<tr>
<td>15</td>
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<td>None</td>
<td>No</td>
<td>R N2b</td>
<td>Bilateral BOT excision</td>
<td>T1: 0.4 cm</td>
<td>R BOT</td>
</tr>
<tr>
<td>16</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>R N2b</td>
<td>Bilateral BOT excision</td>
<td>Tx</td>
<td>NA</td>
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<tr>
<td>17</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>L N2b</td>
<td>Bilateral tonsillectomy, bilateral BOT excision, L partial pharyngectomy</td>
<td>T1: 0.3 cm</td>
<td>L tonsil</td>
</tr>
<tr>
<td>18</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>L and R N3</td>
<td>Bilateral tonsillectomy, bilateral BOT excision, L partial pharyngectomy</td>
<td>T2: 3 cm, 2.2 cm</td>
<td>L BOT, L tonsil</td>
</tr>
</tbody>
</table>

Abbreviations: BOT, base of tongue; GT, glossotonsillar; L, left; NA, not applicable; PE, physical examination; PT, palatine tonsil; R, right.

*Underwent previous biopsy of BOT and either a biopsy of the palatine tonsil or tonsillectomy.

*Underwent isolated biopsy of one site.

Table 5. Pathologic Characteristics of a Subgroup of Patients Without Any Suspicious or Contradictory Findings on Preoperative Workup

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section was performed, suggesting the ineffectiveness of a superficial, focal biopsy of the base of tongue.

Use of imaging to aid in the diagnosis of an unknown primary tumor is common but not standard because 14.9% of patients did not undergo any form of imaging before TORS. The use of CT or MRI allows for identification of anatomical abnormalities, but diagnostic accuracy is highly variable, ranging from 15% to 52%. Despite this, both CT and MRI are useful in nodal staging, and are independent of the examiner.

Previous EUA with random biopsies was not standard either because 18 of 47 (38.3%) underwent a previous biopsy before TORS. In the setting where there are no physical examination or imaging findings, random biopsies of multiple sites are recommended, but this only occurred in 10 of 18 patients in our study. Furthermore, there are inconsistencies between patients undergoing a tonsil biopsy and those undergoing a full tonsillectomy because 6 of the 12 patients (50%) underwent biopsies of the tonsil, despite previous reports indicating a higher detection rate when a formal tonsillectomy is performed compared with a tonsil biopsy.

In concordance with much of the published literature, we noted that the most common location identified for an unknown primary tumor are the base of tongue and the palate tonsil. Both of these locations are easily accessible with a TORS approach. Furthermore, in our study, of the 34 tumors that were successfully identified, 29 had clear margins, suggesting a high rate of definitive therapy with curative intent. Use of TORS for surgical resection of upper aerodigestive tract neoplasms has a high success rate, with unsuccessful resections noted because of inadequate exposure, tumor size, and inexperience.

The size of the primary tumor was variable, with most being 2.0 cm or less; in 3 patients the primary tumor was greater than 2.0 cm. The first patient had a superficial ulceration of the left base of tongue noted on physical examination. In the second patient, the tumor was submucosal, making identification through physical examination and imaging difficult. In the third patient, pathologic examination noted a superficial, spreading, multifocal pattern of disease in the 2 synchronous primary sites identified; one was in the base of tongue and the other was in the tonsil.

Although TORS has been a relatively new technique in the realm of head and neck cancer, multiple published studies have established its safety and feasibility for the management of head and neck cancer. Reported complications include dysphagia, bleeding, airway edema, pharyngocutaneous fistula, aspiration pneumonia, and death. Bleeding rates vary from 0.5% to 10.4%, with our rate falling within the expected range. Dysesthesias secondary to pressure has been reported infrequently, with one event in a case series of 177 patients, but this was not appreciated in our series.

By pooling data from multiple institutions, we were able to increase our sample size and also include a more generalized approach to unknown primary tumors by minimizing single-institution biases. However, the heterogeneity of the database serves as a limitation in that the preoperative workup, operation performed, and surgeon technique varied at each institution. Each institution was provided a standard database for abstraction, but inherent selection and reporting biases limit the generalizability of our results. Currently, we cannot specify which factors associated with TORS are likely to lead to its effectiveness in the localization of an unknown primary tumor. The improved magnification, use of spatulated retractors and wristed instrumentation, and submucosal resection of the base of tongue could all contribute, and to identify which one(s) plays a key role would require further studies.

In conclusion, our results suggest that the use of TORS in the identification of an HNSCC with an unknown primary site is highly efficacious because the detection rate with TORS in the setting of misleading information or negative workup results was superior to what has been reported with traditional EUA with tonsillectomy and random base of tongue biopsies. Preoperative workup continues to be variable regarding types of imaging and outside biopsy specimens obtained, but contrast-enhanced CT or MRI and combination PET-CT are useful tools to aid in the diagnosis. All identified primary tumors were located in the base of tongue or palatine tonsils, and for most, complete resection was feasible through TORS. Thus, this technique allowed for both diagnosis and definitive management of the primary tumor site, which obviates the need for wide-field radiation, theoretically reducing overall morbidity. In addition, in cases with only a single metastatic node without extracapsular extension (eg, T1 N1 M0), a complete resection with clear margins could allow for either single-modality therapy or a reduction in the overall radiation dose. A multi-institutional, prospective trial with a standardized preoperative workup and surgical treatment with TORS is therefore warranted to further investigate the efficacy and cost-effectiveness of this approach in this subgroup of patients.
Analysis and interpretation of data: Patel, Magnuson, Holsinger, Karni, Gross, Ford, Méndez. Drafting of the manuscript: Patel, Holsinger, Richmon, Ferrell, Méndez. Critical revision of the manuscript for important intellectual content: Patel, Magnuson, Holsinger, Karni, Richmon, Gross, Bhrany, Ford, Kennedy, Méndez. Statistical analysis: Patel, Magnuson, Méndez. Administrative, technical, or material support: Holsinger, Richmon, Gross, Kennedy, Méndez. Study supervision: Magnuson, Holsinger, Karni, Richmon, Bhrany, Méndez.

Conflict of Interest Disclosures: Drs Magnuson, Richmon, Gross, and Méndez received honoraria for speaking and/or procuring for Intuitive Surgical. No other disclosures were reported.

Previous Presentation: This study was presented as a poster at the American Head and Neck Society 2013 Annual Meeting, April 10-11, 2013, Orlando, Florida.

REFERENCES

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