A New Paradigm for the Diagnosis and Management of Unknown Primary Tumors of the Head and Neck: A Role for Transoral Robotic Surgery

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**Objectives/Hypothesis:** In 2% to 3% of patients with cancer metastatic to cervical lymph nodes, a primary tumor will not be found despite exhaustive diagnostic efforts. The treatment for these patients includes cervical lymphadenectomy followed by radiation to areas with increased risk of harboring a mucosal primary. Wide-field radiation therapy increases the incidence of xerostomia and dysphagia. Localizing a primary tumor has thus both therapeutic and quality-of-life implications, allowing possible complete surgical excision, concentrated radiation therapy, and potential deintensification of adjuvant therapy. With improved visualization and freedom of motion, transoral robotic surgery (TORS) is an innovative surgical modality that allows resection of oropharyngeal subsites with minimal morbidity.

**Study Design:** Retrospective chart review.

**Methods:** Ten patients with unknown primary tumors of the head and neck were identified. All patients underwent a cervical biopsy, positron-emission tomography/computed tomography, formal endoscopy, and bilateral tonsillectomy. When the initial endoscopy and biopsies did not localize a primary tumor, all patients underwent transoral robotic base of tongue resection.

**Results:** Evaluation of the patients’ oropharyngeal mucosa using the robot did not reveal an obvious lesion and no palpable tumors were appreciated in the resected specimens. In 9/10 (90%) patients, pathologic examination revealed invasive squamous cell carcinoma (SCCA) with a mean diameter of 0.9 cm.

**Conclusions:** Unknown primary SCCA presents a diagnostic challenge to the head and neck surgeon. We present a small series of tumors that would have been treated as unknown primaries under traditional diagnostic and therapeutic algorithms. TORS base of tongue resection identified primary tumors in 90% patients with minimal morbidity.

**Key Words:** Unknown primary, transoral robotic surgery, base of tongue, diagnostic.

**Level of Evidence:** 4.

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**INTRODUCTION**

Cervical metastases from an unknown primary site (CUP) are an uncommon presentation of head and neck squamous cell carcinoma accounting for 2% to 4% of all cases. In the traditional diagnostic paradigm, when a primary tumor site is not readily identified on physical exam, computed tomography (CT) scan, and flexible laryngoscopy, the patient is taken to the operating room for an exam under anesthesia (EUA), with directed biopsies of the most common sites harboring an unknown primary: the nasopharyx, hypopharynx, tonsil, and base of tongue (BOT). The reported diagnostic success of this procedure ranges from 17% to 40%. With addition of positron-emission tomography (PET) and the fusion of PET with CT images, a recent meta-analysis of 11 studies with a total 433 unknown primary patients demonstrated an improved detection rate of 37.5% by adding PET/CT, with a sensitivity and specificity of 84%.

When the available diagnostic modalities fail to detect the primary tumor site, the patient is treated with either primary irradiation to the neck and all potential mucosal primary sites, plus or minus chemotherapy or surgical excision of the neck disease followed by radiation. Due to the relative paucity of cases, no single modality has demonstrated a significant improvement in survival. The 5-year actuarial survival is still dismal: 69% for N1, 58% for N2, and 30% for N3 disease.

Additionally, a more focused radiation field can be employed, thereby sparing much of the pharyngeal tissue from treatment and avoiding many of the untoward, radiation-induced side effects. The reported rates of grade 3 dysphagia and xerostomia following conventional radiotherapy for CUP...
are approximately 50%. Even with the use of intensity-modulated radiation therapy (IMRT) and deintensification to the potential primary mucosal sites, patient morbidity is improved but not insignificantly.\textsuperscript{4, 5}

Transoral robotic surgery (TORS) has emerged over the past few years as a highly efficacious modality for treating oropharyngeal carcinoma with excellent long-term functional outcomes.\textsuperscript{6} With improved visualization and freedom of motion, TORS allows excellent access to the oropharyngeal subsites making it not only useful for ablative purposes, but potentially as a diagnostic modality. A previous precedent has been established for performing complete palatine tonsillectomies over deep tonsillar biopsies during the workup of a CUP.\textsuperscript{7} The rationale is that the crypts present in tonsillar tissue can harbor inconspicuous submucosal tumors. A similar thought process could be extrapolated to the lingual tonsil, which in the past have been difficult to access transorally. Utilizing a transoral robotic approach, we present a novel method for detecting occult BOT primary tumors after the traditional diagnostic paradigm of tonsillectomy, EUA, and random biopsies have failed.

**MATERIALS AND METHODS**

An institutional review board-approved, retrospective chart review was performed on all patients who had undergone a TORS BOT resection for an unknown primary tumor from 2009 to 2011. The charts were reviewed to ensure that only those patients with biopsy-proven cervical squamous cell carcinoma metastases, for whom an office evaluation with flexible laryngoscopy and preoperative imaging (CT, magnetic resonance imaging, and/or PET/CT) failed to identify a primary mucosal site in the upper aerodigestive tract. Further inclusion criteria required that the patient had undergone an EUA, random biopsies of the BOT and pharynx, and tonsillectomy (when appropriate) without identification of the primary site prior to the TORS procedure.

**Description of Procedure**

After obtaining informed consent for the TORS BOT resection and/or neck dissection, the patient is brought to the operating room and placed supine on the operating table. After induction of general anesthesia, the table is turned 180°. First, both palpation of the oropharynx and a direct laryngoscopy are performed to confirm that the mucosal primary site cannot be identified. The BOT is then exposed using either a flat McIvor blade on a Dingman retractor or a Feyh-Kastenbauer retractor depending on the patient's specific anatomy. The da Vinci surgical robot is then docked on the patient's right side and a 30° high-definition, three-dimensional endoscope is introduced. Within the two robotic arms, a 5-mm Maryland grasping forceps is placed through the left port, and the 5-mm monopolar cautery spatula is introduced through the right side. The epiglottis is visualized to ensure resection of the lingual tonsillar tissue down to the vallecula.

An incision is made in the midline of the tongue with the monopolar cautery from the circumvallate papillae toward the vallecula. The incision is carried down to the muscular layer, but not through the muscle to avoid unnecessary trauma. Dissection is carried laterally along the anterior border of the BOT. Once the glossopharyngeal sulcus is reached, the incision is carried down toward the vallecula. To aid in the resection of the entire mucosal surface of the BOT, the assistant provides anterior pressure delivering the tongue base into the field. The tongue musculature is used as the depth limit for resection because a distinct plane for the lingual tonsils does not exist. Once the pharyngoepiglottic folds are visualized, the lateral half of the BOT is removed. The lateral halves of the BOT are then removed separately. The specimens are then oriented for histopathology.

**RESULTS**

Over the past 17 months, 114 patients underwent TORS oropharyngeal resections at the University of Pittsburgh Medical Center. A total of 10 patients met the study inclusion criteria and had undergone a TORS BOT resection. The demographics for these patients are depicted in Table I. The majority of the patients were male with a mean age of 55 years. Three of the patients were heavy tobacco abusers, with only two of those reporting alcohol abuse. The remaining patients denied...
any history of substance abuse. None of the individuals had a previous history of malignancy. All of the patients presented with palpable level II and/or level III cervical nodes, with six of the patients having clinically staged N2a, two N2b, one N1, and one N3 fixed level II-III lymph node.

Preoperative Workup

Four of the patients had undergone open biopsies at an outside facility prior to presentation at our institution. The remaining six patients had received needle biopsies at either our institution or elsewhere. All cytology was reviewed at our institution. Comprehensive head and neck exams and flexible laryngoscopy were performed by at least one attending surgeon without evidence of a mucosal primary site. All patients underwent directed BOT biopsies before the TORS procedure. Some patients underwent biopsies that were submitted for intraoperative pathology consultation, and if negative, the patients underwent TORS BOT mucosectomy. Seven of the patients had already undergone bilateral tonsillectomy as children, and the other three underwent narrow-field tonsil excision during the direct laryngoscopy.

All of the patients had undergone a PET/CT reviewed by a dedicated head and neck radiologist prior to the exam under anesthesia with direct laryngoscopy and biopsies. Minimal [18 F]-fluorodeoxyglucose uptake was seen in the BOT for four of the patients. On final pathologic analysis, all four of these patients were positive for BOT squamous cell carcinoma (SCCA). However, the PET/CT findings implicated the incorrect laterality within the BOT in two of the patients, with a localization accuracy of 50%. The overall sensitivity for PET/CT imaging in our study was 40%.

Results of the TORS BOT Resection

In nine of the 10 patients, a mucosal primary was discovered in the TORS-resected BOT with a mean diameter of 0.9 cm ± 0.65. Seven of the nine carcinoma-positive specimens were <1 cm, ranging from 0.2 to 0.9 cm. Human papillomavirus (HPV)/p16 positivity was found in eight of nine carcinomas (Table I). In one of the eight patients, the primary tumor was located in the contralateral portion of the BOT from the cervical metastases. In the isolated case where the TORS procedure did not identify the primary lesion, the patient had an excisional biopsy at an outside institution of a cystic...
mass, in which a focus of SCCA was identified. The HPV status of the pathologic node was not determined.

Nine patients underwent chemoradiotherapy with IMRT. The remaining patient had a positively identified, completely resected BOT primary and underwent a neck dissection with only one positive node on final pathologic analysis. Therefore, this patient did not receive adjuvant IMRT to the primary site and at-risk nodal basins. The patient whose tumor could not be located underwent primary chemoradiation with IMRT to the entire oropharynx and bilateral cervical nodal basins.

None of the patients in our series had any major intraoperative or postoperative blood loss. Nine of the ten patients were able to tolerate a soft diet at the first postoperative visit. The average weight loss from pre- to postprocedure was 3%. Of the five patients who completed the University of Washington Quality-of-Life survey, the pain scores were either 75 or 100, which corresponds to little or no pain, respectively. The single patient requiring a percutaneous endoscopic gastrostomy tube insertion with long-term alimentation had an HPV-negative, 2-cm submucosal tumor (Table I). The patient was a heavy smoker (60 packs/year) and continued to abuse tobacco throughout his adjuvant chemoradiotherapy treatment. There were no other reported complications from the TORS BOT resection. All patients began their adjuvant therapy within 4 to 6 weeks following the procedure.

DISCUSSION

Patients with cervical metastases from an unknown primary comprise a small percentage of all head and neck squamous cell carcinoma cases, and the number of cases is continuing to diminish over time.\(^1,8\) The decrease in CUP patients has been attributed to improved visualization by the use of endoscopes during EUA and PET/CT imaging. However, even with the addition of PET/CT, the primary tumor location remains unidentified in 45% to 63% of CUP patients.\(^2,9\) Once the diagnostic paradigm of tonsillectomy and directed biopsies with the aid of a PET/CT has failed, the most widely accepted therapeutic option, currently, is radiation often administered with chemotherapy, to the entire Waldeyer’s ring and at-risk cervical nodal basins.

The most common site for an unknown primary is the oropharynx with the tonsil and BOT subsites accounting for 90% of all identified CUP sites.\(^10\) In a study of 87 patients who underwent tonsillectomy as a part of the workup for cervical node metastases presenting as an unknown primary cancer, 26% had a tonsillar primary.\(^11\) With a CUP originating from the tonsil, the contralateral tonsil from the metastatic node was the location of the primary tumor in 10% of cases.\(^12\) Based on our case series, we contend that the majority of the CUPs that are not detected in the tonsils can therefore be found in the BOT. A palatine tonsillectomy is a much more effective method than deep tonsillar biopsies for detecting primary tumors in patient’s with CUP due to the submucosal, inconspicuous nature of these tumors.\(^7\) The TORS BOT resection represents a diagnostic lingual tonsillectomy. The average primary BOT tumor size on pathologic analysis was 0.9 cm, highlighting the difficulty in gross visualization and the importance of careful pathologic analysis. Additionally, similar to the palatine tonsils, the primary tumor was located in the contralateral side in one of the nine tumors (12.5%), suggesting the need for a bilateral lingual tonsillectomy. Removal of both sides is further supported by the well-documented bilateral lymphatic drainage of the BOT.

HPV positivity in a CUP can further direct the clinician toward the primary tumor site. The HPV genome has been detected in 47% to 63% of oropharyngeal SCCA.\(^13,14\) HPV-positive tumors preferentially localize to the lingual and palatine tonsil, which has been attributed to the presence of numerous full-thickness crypts within the tonsillar tissue.\(^15\) The tonsillar crypts are lined by a reticulated, fragile, squamous epithelium facilitating transfer of antigens to the porous basal layer, theoretically predisposing the incomplete, exposed, basement membrane to viral infection and deposition. Additionally, HPV-positive tumors have shown a predilection for nodal metastases at an earlier stage of the primary disease compared with HPV-negative SCCA.\(^16,17\) In a recent study, Desai et al. retrospectively examined metastatic cervical lymph nodes from 41 patients. HPV positivity was found in 44% of patients with oropharyngeal primaries and in four of the five patients with a CUP.\(^18\) No HPV-positive lesions were found in the larynx or hypopharynx. In another study, HPV16 testing was performed on 77 cervical SCCA fine-needle aspiration samples. HPV-positivity was found in 10 of 19 (53%) metastases from oropharyngeal carcinomas and none from any other head and neck SCCA site.\(^19\) The primary tumors were also tested with 11 of the 19 exhibiting HPV-positivity. In our series, eight of the nine patients with BOT tumors demonstrated HPV positivity, with seven of those being subcentimeter lesions. The data suggest that when a tonsillectomy fails to identify the primary site in an HPV-positive CUP, there is a strong likelihood of primary tumor site identification with a TORS BOT resection.

The current accepted treatment paradigm for CUP involves chemoradiation with radiation therapy directed at the at-risk nodal basins and potential mucosal primary sites. The 5-year actuarial survival has been estimated to be 69% for N1, 58% for N2, and 30% for N3 disease.\(^3\) Haas et al.\(^1\) retrospectively studied 57 patients presenting with a CUP and determined that in the patients where the CUP mucosal primary site was detected, the 4-year survival was 100% compared to the 58% for the group where the site remained undetected. These results could have been confounded by the increased number of patients with N3 disease (12 vs. 0) in the undetected CUP patients, but the survival benefit was also seen in the patients with N2a (83% vs. 100%) and N2b (58% vs. 100%) disease. Weir et al.\(^20\) compared survival outcomes of 85 patients treated with radiation to the nodal basins alone, with 59 patients irradiated at both the nodes and potential primary sites. Mucosal tumors emerged in 7% of patients receiving irradiation to the cervical lymph nodes alone versus 1.7% in those...
with irradiation to both potential primary sites and offending nodal basins. The overall nodal relapse rate was 49%, and 5-year survival rate was 41% for all patients. There was, however, no difference in survival or cause-specific survival between the two groups; it is therefore possible that with complete excision of a small BOT tumor, postoperative irradiation could be selectively delivered to the nodal basins, thereby sparing the oropharyngeal structures and possibly reducing morbidity without adversely affecting survival.

The toxicity of chemoradiation for cervical unknown primary results in a grade 3 dysphagia and xerostomia for approximately half of the CUP patients. Even with the use of IMRT, 25% of the patients in the series by Madani et al. had grade 2 xerostomia, 46% developed esophageal stricture, and 95% had a gastrostomy tube for a median of 6 months. A well-established causal relationship exists between the radiation dose to the constrictors and esophageal inlet and long-term swallowing difficulties. Patients in whom >78% of the cricopharyngeus inlet received >60 Gy have a 50% likelihood of developing a stricture. With the identification of the primary site, only one patient in our series required long-term use of an enteral feeding tube. The patient was a heavy smoker (Table I) and had a HPV-negative tumor, both of which have been associated with adverse functional outcomes. The radiation fields were altered in all eight patients, with reservation of the highest doses for the BOT and reduction in the dose given to the constrictors and esophageal inlet. The identification of the primary tumor site through the TORS BOT resection will result in more directed radiotherapy, thereby improving survival and reducing treatment morbidity.

Transoral robotic BOT resections have resulted in good functional outcomes for both oncologic and sleep apnea treatment procedures. In a series of 20 patients treated with BOT reduction for severe obstructive sleep apnea (OSA), there were no major bleeding complications and reported swallowing difficulties. There was no reported significant change in weight or body mass index after the procedure. The OSA BOT reduction procedure described is identical to the TORS BOT resection performed in our study. Leonhardt et al. demonstrated that when TORS was used as an up-front surgical approach alone or in combination with adjuvant chemoradiotherapy, the overall quality of life and functional status returned to baseline levels within 12 months, as measured by the Performance Status Scale for Head and Neck Cancer Patients and Short Form-8 Health Survey questionnaires. Similar to a palatine tonsillectomy, a TORS BOT resection can be considered a safe procedure with minimal morbidity. Finally, our approach has been described in a recent case report with successful identification of the primary tumor.

In 2011, Karni et al. demonstrated the use of transoral laser microsurgery (TLM) as a method of occult primary detection in CUP patients. Similar to our series, the authors were able to identify an oropharyngeal primary in 17 of 18 patients (94%) utilizing TLM. The described technique involves inspecting the palatine and lingual tonsillar tissue with a microscope or endoscope, and incising any suspicious lesions with a CO₂ laser. Based on the appearance and palpation of the incised tissue, a frozen section biopsy is sent to confirm pathologic diagnosis. If this fails to demonstrate an occult primary, an ipsilateral palatine tonsillectomy and BOT resection is performed through TLM. Of the TLM-identified primary tumors, 37% were located in the palatine tonsils and 63% in the BOT. Disease-free survival (DFS) was compared between the TLM group and a traditional EUA cohort of 12 patients. The traditional EUA patients had a recurrence rate of 41.6% and a DFS of 44%, with the TLM patients exhibiting no recurrences and a 100% DFS. The findings of this study reinforce the results seen in our series: through the use of minimally invasive transoral surgical resection, a mucosal primary can be found in the vast majority of CUP patients in the oropharyngeal tonsillar tissue with a significant improvement in survival outcomes.

The question can be posed whether in an HPV-positive cervical unknown primary metastasis, can the radiation fields simply be altered to include only the oropharyngeal subsites and avoid the naso- and hypopharynx? In a recent study by Maxwell et al., HPV positivity was demonstrated in four out of five nonkeratinizing nasopharyngeal carcinomas. Based on these data, without localization of the primary tumor, the entire oropharynx and nasopharynx should be irradiated for a CUP. By identifying the primary tumor through a minimally invasive transoral procedure, the nasopharynx and other oropharyngeal subsites (tonsils, posterior pharyngeal wall, soft palate) can be effectively spared from radiation-induced mucosal and muscular damage, thereby improving both functional and survival outcomes.

CONCLUSION

Cervical SCCA from an unknown primary poses a difficult diagnostic challenge despite advances in fiberoptics and imaging. PET/CT, although demonstrating a clear improvement in detection when added to the traditional paradigm, still fails to isolate the primary tumor in more than half of CUP patients. Identification of the primary mucosal malignancy has shown significant therapeutic impact with a vast improvement in 5-year survival rates and a potential reduction in patient morbidity by saving radiation toxicity to the other pharyngeal subsites. Through the use of a TORS conservative BOT resection, we present a small case series illustrating a highly efficacious and reproducible technique for detecting subcentimeter, HPV-positive, BOT primaries in cervical unknown primary patients for whom the traditional diagnostic paradigm has failed.

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