Role of Transoral Robotic Surgery in the Work-up of the Unknown Primary

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KEYWORDS

• Unknown primary • Tongue base mucosectomy • Lingual tonsillectomy
• Transoral robotic surgery

KEY POINTS

- Transoral robotic surgery may be used to increase the diagnostic yield of identifying a primary tumor in the tongue base.
- Identifying a primary tumor may help tailor radiotherapy volumes or eliminate pharyngeal radiotherapy in patients whose primary tumors are completely excised.
- A small percentage of primary tumors may be identified in the contralateral pharynx or with multiple primary sites, which may require intensive adjuvant therapy.

INTRODUCTION/HISTORY/DEFINITIONS/BACKGROUND

Head and neck squamous cell carcinoma of unknown primary site (CUP) comprises a relatively small proportion of all head and neck cancers. The historical diagnostic work-up for these tumors included clinical examination, imaging of the head and neck, and operative examination under anesthesia, which includes a panendoscopy and directed biopsies of suspicious sites with palatine tonsillectomy. Imaging with fludeoxyglucose [1] fluorodeoxyglucose (FDG)-PET as well as new surgical diagnostic techniques, such as transoral lingual tonsillectomy with robotic or laser-assisted technology may improve the likelihood of identifying a primary tumor. This article reviews the role of transoral robotic surgery (TORS) in the diagnostic evaluation and therapeutic paradigm in the management of CUP and hidden, small-volume oropharyngeal cancers.

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Otolaryngol Clin N Am 53 (2020) 965–980
https://doi.org/10.1016/j.otc.2020.07.008 **oto.theclinics.com**
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DISCUSSION

Epidemiology

CUP is a rare disease entity accounting for only 1.5% to 9% of all head and neck cancers.[2–4] Historically, patients with CUP were believed to harbor either a small occult malignancy in a putative mucosal site, such as the tonsil, tongue base, piriform sinuses, or nasopharynx, or to have a primary tumor that has involuted over time due to an antitumor response by the immune system.[5] Recent studies, however, have shown that a vast majority of patients who present with an unknown primary and metastatic nodal disease and who ultimately have a primary tumor identified at the time of operative examination under anesthesia have a primary tumor in the oropharynx.[6] In a study by Cianchetti and colleagues,[6] 89% of all tumors eventually identified were in the oropharynx, of which 45% were in the tonsil and 44% were in the tongue base.

Like oropharyngeal squamous cell carcinomas (OPCs), CUP commonly is associated with the human papillomavirus (HPV).[7–9] Although it has not been demonstrated clearly in population-level studies, it is likely that the rising incidence of OPC is paralleled closely in CUP.[10] One multi-institutional study demonstrated that the prevalence of HPV-mediated CUP has risen over time.[11] This finding is consistent with the observation that HPV-mediated oropharyngeal cancers typically present with larger nodal burden than HPV-negative oropharyngeal cancers,[12] further supporting the notion that CUP is increasing in incidence.

Diagnostic Work-up

Nodal biomarkers

With the recent changes in the 8th edition of TNM staging by the American Joint Committee on Cancer and the Union for International Cancer Control, patients with CUP potentially are assigned a specific anatomic site based on their nodal biomarker status.[13] Patients whose lymph nodes indicate HPV-mediated disease by overexpression of the tumor suppressor protein p16 (cyclin-dependent kinase 2A) on immunohistochemistry may harbor a possible HPV-mediated primary tumor in the oropharynx. Studies have shown, however, that other primary sites, such as cutaneous primaries, may overexpress p16.[14] Because non-HPV–mediated cancers also may overexpress p16, confirmatory testing with in situ hybridization should be performed. In this setting, a T0 category of the oropharynx is assigned after careful evaluation of the patient with examination, imaging, and biopsies to rule out a primary. Similarly, patients with nodal disease that stains positive for Epstein-Barr virus–encoded RNA (EBER) may harbor a nasopharyngeal primary and, if examination, imaging, and biopsies are negative, they are assigned a nasopharyngeal primary site. Patients whose lymph nodes are negative for both biomarkers cannot be assigned a primary tumor site. Nodal biomarkers may have both diagnostic and therapeutic implications. These biomarkers may help surgeons direct diagnostic biopsies and/or excisions as well as radiation oncologists tailor their treatment volumes. Future research in novel biomarkers, such as nodal microRNA, may further help predict and localize primary tumors by tumor subsite.[15]

Axial Imaging (Computed Tomography and Magnetic Resonance Imaging)

All patients with a head and neck malignancy should routinely undergo axial imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI). These imaging modalities may reveal subtle anatomic abnormalities that may help guided surgical biopsy at the time of operative endoscopy. These modalities are limited, however, in that many occult neoplasms may be hidden in small crypts of Waldeyer ring. One study reported a sensitivity, specificity, positive predictive value, and negative predictive value of 70%, 62%, 84%, 42%, respectively, for conventional

imaging.[16] Specific sequences on MRI, such as diffusion-weighted imaging, may help improve diagnostic properties, although further research is needed to confirm these findings.[17]

Ultrasound

A recent guideline issued by the French Society of Otorhinolaryngology recommended the use of ultrasound in the setting of unknown primary in order to characterize and evaluate lymph nodes architecture as well as the thyroid gland to rule out a primary tumor in the thyroid and to evaluate cystic or necrotic components of a node that may further point to a oropharyngeal primary lesion.[18] Small series also have demonstrated that transcervical ultrasound may be used to identify small tongue base primary tumors.[2,19] In a single-institutional case series, in patients with no primary lesion identified on PET, ultrasound identified a hypoechoic target in 9 out of 10 patients, most of whom were in the tongue base, and of whom 7 eventually were identified by biopsy.[19] Further larger-scale evaluation of this approach may be needed.

PET/Computed Tomography

The advent of functional imaging with FDG PET/CE has improved the ability to identify candidate primary tumor sites in patients presenting with unknown primary carcinomas. In 1 systematic review and meta-analysis of 28 studies and 910 patients, the detection rate, sensitivity, and specificity of PET/CT were 29%, 78% and 79%, respectively.[20] In a subsequent systematic review and meta-analysis of 7 studies and 246 patients with unknown primary and cervical nodal metastases, the detection rate, sensitivity, and specificity were 44%, 97%, and 68%, respectively (**Table 1**).[21] In these studies, care must be taken in interpreting a high test sensitivity because this property may be artificially inflated in cases of no primary tumor found at the time of operative examination under anesthesia. A false-negative test is a test in which a PET/CT does not reveal a primary tumor and one is found at the time of operative examination under anesthesia. As such, when techniques, such as panendoscopy alone, are employed, fewer tumors are found at the time of operative examination under anesthesia. A more representative measure of the test properties is the diagnostic identification rate of a primary tumor.

Another caveat to interpretation of PET/CT imaging is that they may be associated with false-positive test results and lack specificity. The lingual tonsil commonly is an anatomic site with PET avidity and this may lead to misinterpretation of a primary site. In the former of the 2 meta-analyses, primary tumors identified in the tongue base on PET were associated with false-positive rate of 28.6%.[20] Furthermore, the same investigators suggest that PET exhibits a lower sensitivity for identifying primary tumors of the tongue base (68%) and tonsil (76%), respectively. Taken together, these data suggest that although PET/CT may provide additional information compared with

Table 1
Diagnostic test properties for evaluation of the unknown primary

	Sensitivity	Specificity	Identification Rate
Panendoscopy and tonsillectomy[22]	N/A	N/A	31% in PET-negative patients
Tonsillectomy[24]	N/A	N/A	34%
PET[20,21]	78%–97%	68%–79%	29%–44%
NBI[26,27]	74%–83%	76%–88%	32%–35%
TORS/TLM-guided approach[36,38]	N/A	N/A	70%–78%

physical examination and conventional imaging in order to inform potential biopsy targets at the time of operative examination under anesthesia, this imaging modality still may not replace biopsy confirmation of a primary site in order to determine therapeutic targets.

Pandendoscopy and Biopsy

Traditional work-up of the unknown primary involves operative examination under anesthesia with a combination of different endoscopic techniques, such as nasopharyngoscopy, laryngoscopy, esophagoscopy, and bronchoscopy. Regardless of the endoscopic instruments used, the ultimate goal is to carefully evaluate the putative mucosal sites of the upper aerodigestive tract, including the nasopharynx, oropharynx, larynx, and hypopharynx, to rule out a primary in one of the putative mucosal sites. This examination involves direct visualization and palpation, where possible. Surface irregularities, such as erythema, prominent vasculature, and ulceration, may help identify targets for biopsy. A systematic approach is required with careful evaluation of the palatine tonsil and pillars, glossotonsillar sulci, tongue base, vallecula, piriform sinuses, and postcricoid space. The evaluation may be informed by findings on nodal biomarkers (eg, p16 and EBER status of the node) or by areas of PET avidity. Primary tumors may be hidden in the tonsillar crypts or lymphoid tissue or have significant submucosal extension and palpation may help identify these tumors that may escape visual identification. Targeted biopsies of irregular areas based on a combination of the inspection, palpation, and PET findings may help identify a primary tumor. In a recent study, a primary tumor was found at the time of panendoscopy even in 32 of 103 (31%) patients with a negative PET scan.[22,23] Of the primary tumors identified, a majority were in the palatine tonsil (56%), with a smaller proportion identified in the tongue base (25%), likely due to the fact that the investigators performed bilateral palatine tonsillectomy at the time of panendoscopy if no primary tumor was identified with panendoscopy.

Palatine Tonsillectomy

Palatine tonsillectomy has been incorporated as part of the standard work-up of the unknown primary carcinoma with cervical nodal metastases. Clinical practice guidelines from the National Comprehensive Cancer Network recommend routine palatine tonsillectomy in patients who present with metastatic squamous cell carcinoma to lymph nodes in the upper neck (levels I, II, II, and upper V).[22] A recent systematic review and meta-analysis summarized results from 14 studies and 673 patients of whom 416 underwent palatine tonsillectomies. The overall primary tumor detection rate in this study was 34%, of which 89% were ipsilateral, 10% synchronous bilateral and 1% unilateral.[24] These data suggest that providers should consider bilateral palatine tonsillectomy or comprehensive sampling of the contralateral palatine tonsil in the work-up of the unknown primary carcinoma. Deep biopsies of the tonsil alone may not be adequate if they are negative, and surgeons evaluating these cancers should consider complete palatine tonsillectomy on the ipsilateral side at least and possibly bilateral palatine tonsillectomy. Waltonen and colleagues[25] demonstrated that the likelihood of finding an occult primary in the tonsil with deep biopsy alone was 3% compared with 29% with complete excision of the palatine tonsil. These findings were confirmed in a subsequent meta-analysis where the odds ratio of finding a primary was more than 10-fold higher in patients undergoing tonsillectomy compared with those undergoing deep biopsies.[24] If a lesion is suspected, however, based on visualization or palpation, a deep biopsy may be performed to identify the primary tumor. This approach with deep biopsy first of suspicious lesions prior to palatine

tonsillectomy may be preferable, particularly in the setting when one may consider definitive surgical resection through a transoral approach.

Narrow Band Imaging

Narrow band imaging (NBI) is an adjunctive technique to standard white light illumination of surface anatomy. With this technique, white light illumination through an endoscope can be filtered, such that all but 2 wavelengths, 1 band centered at 415 nm and a second band centered at 540 nm.[26] The former of these 2 bands may penetrate the superficial mucosa to visualize submucosal capillaries and is visualized as a brown color whereas the latter penetrates through the submucosal layer to visualize prominent vessels as a cyan color.[26] Data from previous systematic review and meta-analysis suggest that the use of this imaging modality is associated with a pooled sensitivity of 74% and pooled specificity of 86% across 4 studies.[26] Based on this systematic review, however, the identification rate of primary tumors across 5 studies was 36 of 144 (32%), suggesting that many small primary tumors may be missed with this technique. These data were corroborated in an updated systematic-review and meta-analysis published a by another group demonstrating a pooled detection rate, sensitivity, and specificity of 35%, 83%, and 88%, respectively, across 5 studies and 169 patients.[27] Perhaps one of the biggest benefits of NBI is the ability to offer this technique as an adjunctive office-based procedure that may guide biopsies and rapid detection and thus may avoid operative intervention.[28]

Lingual Tonsillectomy

Several cases series have demonstrated incremental benefit of the addition of a transoral lingual tonsillectomy to the traditional operative diagnostic work-up of the unknown primary.[29–35] In these case-series, the addition of lingual tonsillectomy either with a transoral laser microsurgery (TLM) or a TORS approach resulted in improved identification of an occult primary tumor. Preliminary reports described that that many of these unknown primary tumors may be harbored in the tongue base. Karni and colleagues[29] demonstrated that with a TLM approach, an occult primary can be found in 94% of cases, of which 63% were identified in the tongue base. This finding was corroborated by a subsequent series demonstrating that with a TORS lingual tonsillectomy in patients that have previously not had a primary tumor identified with conventional work-up, the detection rate of an occult primary tumor was 90%.[30] Subsequent systematic reviews by our group and others have demonstrated that a transoral lingual tonsillectomy and mucosal resection may identify a primary tumor in 70% to 78% of cases.[36–38] Even in the absence of suspicious findings on clinical examination, axial imaging and PET, a primary tumor may still be found in 64% to 67% of cases.[36,37]

Extent of Lingual Tonsillectomy A lingual tonsillectomy typically is defined by mucosal and lymphoid resection of the superficial surface of the tongue base starting at the circumvallate papilla anteriorly and extending posteriorly to the vallecula with the lateral extent of the excision extending bilaterally to the glossotonsillar sulci. Typically, the deep plane of resection is the plane between the lingual tonsillar tissue and the tongue base musculature. Some consideration may be given, however, to minimal muscular resection in order to avoid positive deep margins if a definitive removal is planned. Different surgeons advocate different approaches ranging from an ipsilateral or hemilingual tonsillectomy to subtotal to total lingual tonsillectomy. The decision to proceed with a less than total lingual tonsillectomy assumes that a vast majority of primary tumors are located on the side of the nodal burden, assuming that the patient

presents with unilateral lymphadenopathy. Secondly, the decision to avoid extensive mucosal and lymphoid resection is to minimize postoperative pain and the possibility of downstream pharyngeal stenosis.

Emerging data, however, suggest although a hemilingual tonsillectomy may identify a majority of primary tumors, that contralateral and midline tumors may be missed or incompletely excised. Geltzeiller and colleagues[39] demonstrated that the identification rate with bilateral lingual tonsillectomy is 80% compared with 68% in patients undergoing a unilateral hemi lingual tonsillectomy. In patients undergoing bilateral lingual tonsillectomy, a primary tumor was found on the contralateral side in 12% of patients.[39] As such, incremental detection rate must be weighed against the added morbidity of the procedure when deciding on a subtotal versus a total lingual tonsillectomy.

Rationale for Lingual Tonsillectomy Because of the relatively small size of the majority of tumors identified in the tongue base by a lingual tonsillectomy, it is conceivable to achieve a negative margin resection with this diagnostic procedure. In 1 systematic review, the positive margin rate after diagnostic lingual tonsillectomy was 19%.[38] In a large single-institutional series, however, the rate of positive margins was 49%, with a majority of positive margins occurring at the deep margin.[39] For this reason the authors' institutional practice is to take a small margin of muscle during the resection to minimize this risk of a positive margin.

The authors' group has further shown that if a small-volume (T1) tongue base primary tumor is identified, and a patient requires adjuvant therapy for close or positive margins to the primary tumor, the size of the radiation volumes is significantly less than in patients where the tumor is treated as a true unknown primary (T0) and the patient receives elective radiotherapy to the pharyngeal axis.[40] Furthermore, recent retrospective studies have shown that in patients who had an extensive diagnostic work-up to investigate an known primary with a TORs approach, and in whom no primary tumor was identified (ie, T0 tumors), avoidance of elective radiotherapy to the pharyngeal axis is associated with similar local control as those who received elective radiotherapy to the pharyngeal axis.[41,42]

Lingual Tonsillectomy in Human Papilloma Virus–Negative Unknown Primary Although it is unclear at the present moment whether transoral lingual tonsillectomy is equally effective in identifying a small-volume primary tumor in the tongue base in patients with HPV-negative disease, 1 recent study suggests that the likelihood of identifying a primary tumor is low (13%) in patients with HPV-negative disease.[43]

Therapeutic Considerations for Transoral Robotic Surgery for Unknown Primary

TORS also may be used as a therapeutic procedure for patients presenting with an unknown primary. In patients with a primary tumor identified at the time of diagnostic endoscopy, a definitive resection may be performed. For example, if a primary palatine tonsil is identified by intraoperative biopsy, a definitive TORS pharyngectomy can be completed in addition to a neck dissection. In patients where no obvious primary tumor is identified at the time of examination under anesthesia, excision of the palatine tonsil on the side of the disease may be considered and evaluating the contents of the tonsil evaluated with intraoperative serial frozen sectioning of the tonsil (ie, bread-loafing). Then, a therapeutic procedure may be considered if a primary tumor is identified on frozen section analysis. In the authors' institutional clinical trial, procedures are offered for patients with limited nodal disease and in the absence of

radiographic signs of extranodal extension so as to minimize the need for adjuvant concurrent chemoradiotherapy.

Radiotherapy Considerations for Management of the Unknown Primary

The management of the unknown primary with radiotherapy, much like the diagnostic surgical work-up, is heterogenous. Many experts advocate elective radiotherapy to putative mucosal sites and the neck.[43] The exact mucosal targets vary across institutional practices, although many would advocate elective mucosal radiotherapy to high-risk targets, depending on nodal biomarkers (eg, nodal p16 and EBER status), risk factors, such as smoking status, ethnicity, and other features. For patients with EBER-positive nodes, radiotherapy target volumes include the nasopharynx and bilateral neck nodes. For patients with p16-positive nodes and a suspected oropharyngeal primary, radiotherapy target volumes include at least the mucosal surfaces of the oropharynx and the lymph nodes of the neck.[44] When no primary site is suspected based on nodal biomarkers and other clinical and demographic features, a primary tumor typically is suspected in the oropharynx, larynx, or hypopharynx. Some studies suggest that, in these cases, unilateral neck radiotherapy may be feasible in patients with limited nodal disease (eg, patients with a single node <6 cm).[44] It is still unclear, however, if patients treated in this manner may be at increased risk of contralateral nodal failures,[45] although in selected series unilateral techniques may offer similar disease control in carefully selected patients.[46–48] Delivery of radiotherapy to the mucosal sites also is variable between institutions, with some providers avoiding elective radiotherapy to candidate mucosal sites,[46] whereas others perform elective radiation to mucosal surfaces.[45] Even if mucosal targets are not deliberately covered, however, nodal targets may result in coverage of the lateral tonsil and tongue base between 50 Gy and 60 Gy.[46]

Treatment Toxicities

Transoral robotic lingual tonsillectomy is associated with a risk of hemorrhage approximately 5%.[36,37] In 1 systematic review, only 1 procedure-related mortality was reported in 556 patients who underwent either a TORS-based or TLM-based diagnostic evaluation.[37] Other complications include tongue sensitivity and numbness, hospital readmission due to pain, and dehydration.[37] Tracheostomy tubes typically are not required and no tracheostomies were required in 220 patients reviewed, whereas 2 of 300 patients reviewed (0.7%) required a gastrostomy tube.[37]

Although there is a scarcity of long-term outcomes with this approach, 1 study demonstrated a deterioration of eating and social disruption domains of the Head and Neck Cancer Inventory at 1 year after completion of treatment, whereas speech and appearance remain similar to baseline.[49]

Avoidance of radiotherapy to the pharyngeal axis in patients with T0 tumors or in patients with primary sites excised and with clear margins may reduce the overall treatment-related toxicity. Preliminary evidence from single institutional studies demonstrates that radiotherapy can be avoided to the pharyngeal axis in patients with true unknown primaries or with primaries excised with margins greater than or equal to 2 mm.[41,50] These approaches may be associated with less requirement for narcotic medication, fewer feeding tubes, less mucositis and fewer unplanned treatment-related hospitalizations.[41]

Treatment Paradigm

Incorporation of transoral techniques, such as TORS or TLM, to increase the diagnostic yield depends on the availability of this technology and a multidisciplinary

discussion on how this technology may benefit each individual patient. This discussion must weigh the burden of nodal disease, the potential benefit of identifying a hidden primary tumor, and the side effects of incremental surgery. Fig. 1 describes a potential treatment algorithm that accounts for these various factors. In patients with advanced nodal disease such as nodes greater than 6 cm or bilateral lymphadenopathy, the incorporation of a lingual tonsillectomy as a diagnostic procedure may help to tailor pharyngeal radiation or avoid it altogether if the tumor is completely excised. This, however, must be weighed against the potential harm of surgery with short-term discomfort as well as the potential delay of proceeding with definitive chemoradiotherapy. If a lingual tonsillectomy were incorporated with neck dissection(s), the added morbidity of neck dissection(s) in patients who are likely to received chemoradiotherapy in the adjuvant setting must be weighted. Results of current and future clinical trials will help define algorithms for management of patients based on extent of disease and with the goals of reducing treatment toxicity and maintaining disease control.

Disease Prognosis

Patients presenting with CUP generally have a good prognosis. As with oropharyngeal cancer, patients with HPV-mediated CUP have a better prognosis than those with HPV-negative disease. In patients with HPV-positive disease and in whom no primary is identified, the prognosis is similar to those patients with small-volume tongue base tumors, with a 3-year survival of 91% in 1 study.[40] Studies have suggested that there is no difference in survival when comparing patients in whom a primary is found and those in whom a primary is not found.[40,51,52]

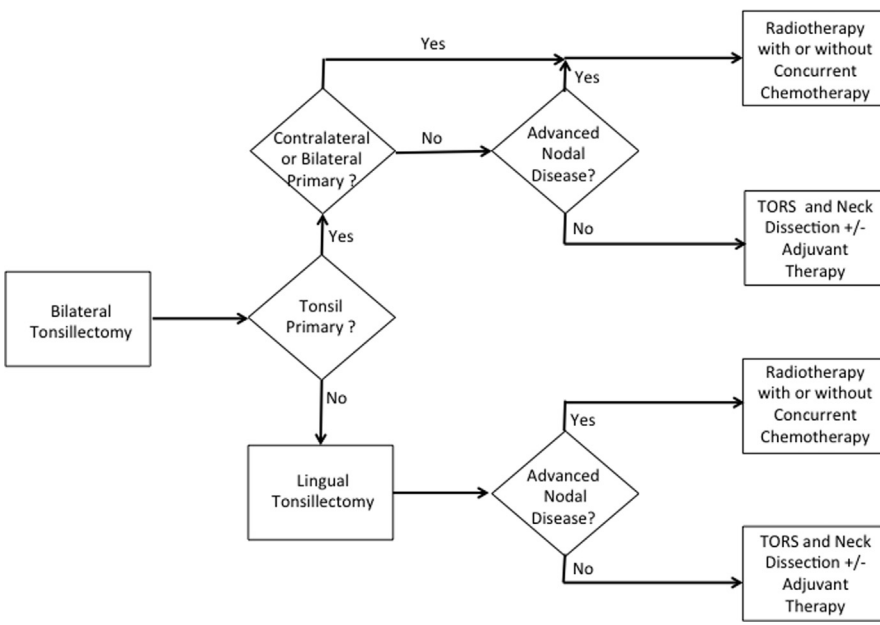

Fig. 1. A management algorithm for the management of patients presenting with metastatic disease to the neck with no obvious primary tumor.

CASE PRESENTATIONS

Case 1

Clinical presentation

A 66-year-old gentleman with a 50 pack-year smoking history presented with a left-sided neck mass and a CT scan showing a 3.6-cm × 1.9-cm left neck mass with no obvious primary tumor (Fig. 2). A fine-needle aspiration revealed metastatic squamous cell carcinoma and p16 status could not be determined. He underwent a left tonsillectomy and panendoscopy by another head and neck surgeon and no primary tumor was identified. Further imaging with an MRI reported an asymmetric right palatine tonsil and subtle asymmetry in the left lateral tongue base. A PET scan reported PET avidity in the left tongue base with a standardized uptake value (SUV) of 7.5.

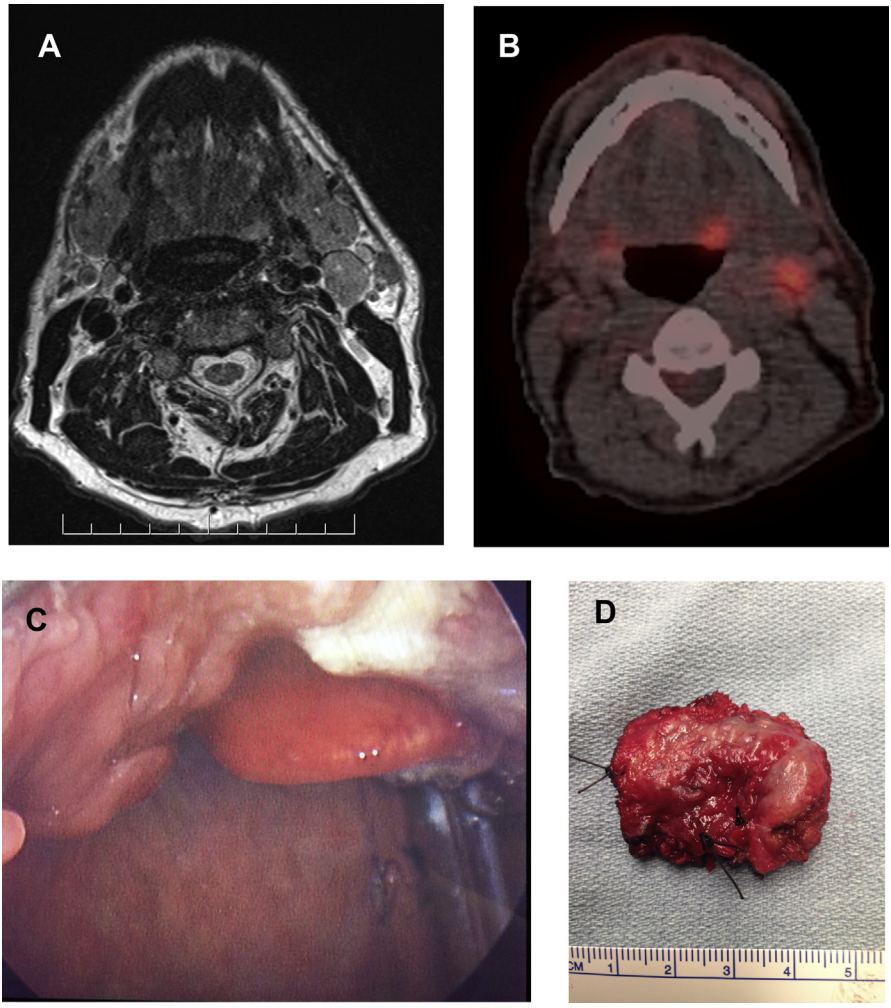

Fig. 2. (*A*) MRI scan of patient presenting with an unknown primary. (*B*) PET/CT. (*C*) Visualization of a suspicious primary site at the time of panendoscopy/examination under anesthesia. (*D*) Resection specimen after transoral robotic tongue base resection.

The patient underwent an examination under anesthesia where a small lesion identified in the left lateral tongue base was biopsied and confirmed to be the primary tumor. The patient underwent a TORS left tongue base resection and left neck dissection. The final pathology demonstrated a 1.2-cm primary tumor with lymphovascular invasion, no perineural invasion, and circumferential clear margins (>5 mm). He had a single metastatic node out of 46 nodes excised measuring 2.7 cm with no extranodal extension. He did not receive adjuvant therapy and has been free of disease for 3 years.

Discussion

The definition of CUP is highly variable and depends on the expertise of the clinicians evaluating the patient, the absence of a clear primary tumor on clinical examination and on imaging. In this case, the patient was previously evaluated with a panendoscopy and imaging at an outside institution but subsequently was noted to have highly suspicious MRI and PET findings, which were confirmed at the time of a second examination under anesthesia. Because of limited primary site disease and nodal disease, this patient was treated with surgery alone.

Case 2

Clinical presentation

A 49-year-old gentleman with a 40 pack-year smoking history presented with a rapidly enlarging right neck mass (Fig. 3). On clinical examination, he had a soft tissue mass measuring 7 cm with skin invasion and muscle invasion. A fine-needle aspiration biopsy confirmed p16-positive metastatic squamous cell carcinoma. An MRI demonstrated a 5.7 $\times$ 5.1 coalescent neck mass invading the sternocleidomastoid muscle and external skin but no visible primary tumor. PET imaging demonstrated FDG avidity, measuring with an SUV measuring 13.2 in the right with a coalescent mass measuring 6.6 cm $\times$ 4.5 cm. No obvious primary tumor was seen. Given the extent of his nodal disease and concern about regional control with definitive chemoradiotherapy, he underwent an upfront surgical approach with radical neck dissection with skin excision and soft tissue reconstruction and a lingual tonsillectomy. His final

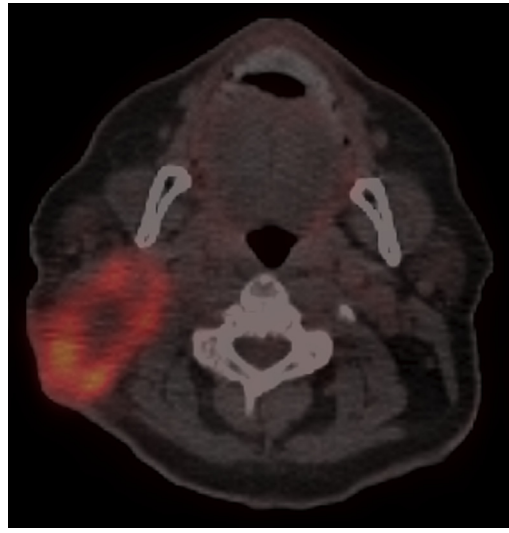

Fig. 3. PET/CT of patient with advanced nodal disease and no obvious primary tumor.

pathology demonstrated a 9-mm right tongue base tumor with the closest margin 3 mm on the lateral deep margin. His nodal dissection revealed 5/38 positive nodes with clear soft tissue margins but major extranodal extension. He underwent planned adjuvant chemoradiotherapy. He has been disease-free for 15 months.

Discussion

In this case, management of the nodal burden and regional control are likely the most important goals of care. With N3 disease at presentation, the authors' multidisciplinary opinion was to treat the patient with triple-modality treatment and with surgery upfront. The addition of a lingual tonsillectomy helped confirm the primary site and, in this case, definitively resect it.

Case 3

Clinical presentation

A 53-year-old otherwise healthy lady with a 25 pack-year smoking history presented with a p16-positive metastatic squamous cell carcinoma to the left neck (Fig. 4). The MRI scan demonstrated metastatic node with radiographic extranodal extension. A PET/CT demonstrated FDG uptake in the left neck nodes and asymmetric uptake in the left palatine tonsil with a maximum SUV of 9.1 in the left palatine tonsil and 8.0 in the right. She underwent bilateral palatine tonsillectomy, which were negative for malignancy, and subsequently underwent a lingual tonsillectomy and left neck dissection. No primary tumor was found. Her neck dissection pathology revealed 1 out of 53 nodes, the largest measuring 4.3 cm with no extranodal extension. She underwent adjuvant therapy to the left neck alone sparing the pharyngeal axis and is disease-free at 12 months post-treatment.

Discussion

In this case, the challenges of interpreting a PET/CT are illustrated. This patient demonstrated PET avidity in both palatine tonsils arguably suggestive of either an

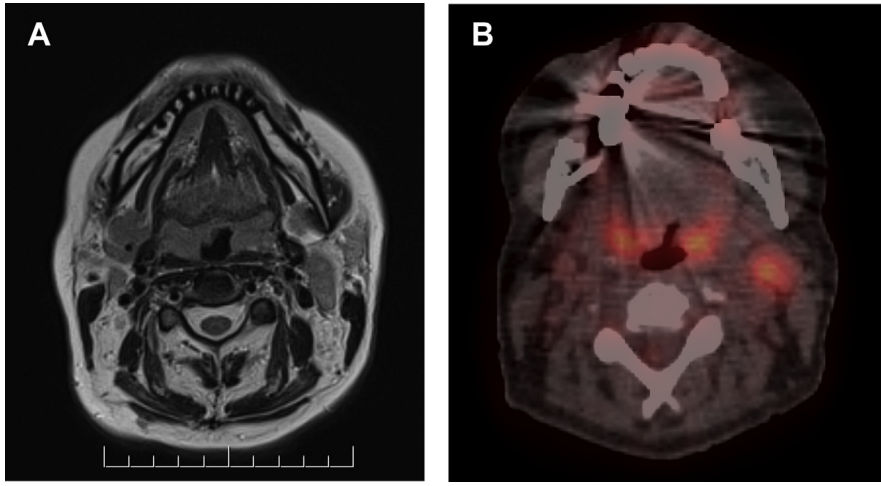

Fig. 4. (*A*) MRI scan of patient presenting with large volume palatine and lingual tonsil tissue with suspicious primary site on the side of nodal disease. (*B*) PET/CT of the same patients showing PET avidity in the both palatine tonsils with mild asymmetric uptake on the side of the nodal disease.

ipsilateral primary tumor in the palatine tonsil or bilateral tonsil primaries. Similar PET avidity was noted in the lingual tonsil. This case demonstrates the challenges of interpretation of PET/CT in the absence of a tissue evaluation. In this case, no primary tumor was found and the pharyngeal axis was spared radiotherapy. This approach is not universally accepted as a standard of care and may require further study.

Case 4

Clinical presentation

A 65-year-old man suffering from atrial fibrillation and history of transient ischemic attacks and a 10 pack-year smoking history presented with a biopsy-confirmed p16-positive left neck mass (Fig. 5). An MRI demonstrated multiple left neck nodes, the largest of which measured 3.2 cm × 2.2 cm, with other 0.7-cm and 0.8-cm nodes in levels 2a/b and 3, with no evidence of extranodal extension with no obvious primary tumor. PET/CT demonstrated metabolically active level 2/3 nodes and asymmetric uptake in the left tongue base suspicious for a left tongue base primary. The patient underwent a palatine tonsillectomy with intraoperative frozen section analysis, which failed to identify a primary tumor. The patient then underwent a lingual tonsillectomy and left neck dissection. The final pathology identified a palatine tonsil tumor measuring 8 mm and involving the deep margin and a separate 0.4-cm contralateral right tongue base primary tumor with the closest margin measuring 3 mm posteriorly. There were 4 positive metastatic nodes in the left neck out of 50 removed, the largest of which was 3.5 cm with major extranodal extension greater than 2 mm. The patient received bilateral neck and pharyngeal irradiation with concurrent chemotherapy in the adjuvant setting. He has been disease-free for 3 months.

Discussion

This case demonstrates the potential intensification of treatment with a surgical approach incorporating transoral techniques. If this patient had undergone a tonsillectomy and panendoscopy alone, an ipsilateral primary tumor would have been identified and the patient then treated with radiotherapy. Instead, with a lingual

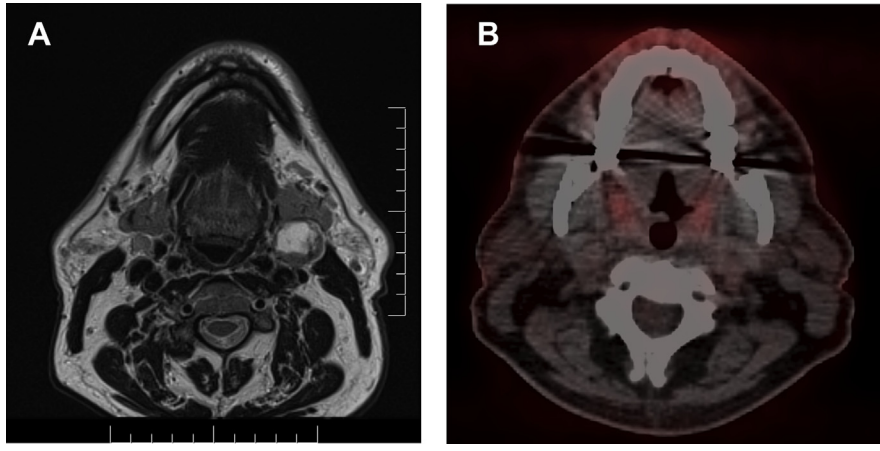

Fig. 5. (*A*) MRI scan of patient with left-sided nodal disease and no obvious primary site. (*B*) PET/CT of the same patient with a report suggestive of a tongue base primary tumor. The final pathology demonstrated a palatine tonsil and contralateral tongue base synchronous primary tumors.

tonsillectomy, a synchronous tongue base tumor was identified and extranodal extension identified at the time of neck dissection and as such required adjuvant chemoradiotherapy.

SUMMARY

Transoral techniques, including lingual tonsillectomy, may improve the identification of primary tumors in patients presenting with unknown primary squamous cell carcinomas of the neck. The increase in the identification rate of these tumors may be associated with short-term morbidity of pain and risk of bleeding. Toxicity must be weighed against the long-term benefits and the potential to spare mucosal radiation. Further trials may help better define the risks and benefits of these techniques.

CLINICS CARE POINTS

- Transoral techniques, such as TORS and TLM, may increase the identification rate of hidden primary tumors in the oropharynx to more than 70%.
- The addition of a lingual tonsillectomy may be associated with short-term pain, acute swallowing impairment, risk of bleeding, and potentially longer hospital stay.
- Identifying these tumors may help to tailor adjuvant therapies and reduce radiotherapy volumes to the pharyngeal axis and, in some instances, avoid radiotherapy altogether.
- Preliminary case series suggest that incorporating transoral techniques is associated with disease control rates similar to those with standard panendoscopy and tonsillectomy as part of the diagnostic work-up.

DISCLOSURE

The author has nothing to disclose.

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