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Transoral robotic approach to carcinoma of unknown primary

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Abstract

Background—The management of carcinoma of unknown primary (CUP) is one of the challenging conditions in head and neck oncologic surgery. Despite various diagnostic tools, the primary tumor site in more than half of cases remains unidentified. The purpose of this study was to assess the feasibility and efficiency of utilizing transoral robotic surgery (TORS) for the diagnosis and treatment of CUP in the head and neck.

Methods—In this prospective, single-institutional, clinical TORS trial, 22 of 181 patients were treated for CUP between 2008 and 2012.

Results—Among all those 22 patients, primary tumor site identification and complete tumor removal was achieved in 17 patients (77.3%) with TORS. Tonsil (59.1%) and base of tongue (18.1%) were identified as the most common tumor locations.

Conclusion—Together with panendoscopy, directed biopsies, and positron emission tomography (PET)/CT, TORS is a valuable option in the identification and treatment of primary tumor sites.

Keywords

carcinoma of unknown primary; transoral robotic surgery; daVinci

INTRODUCTION

Squamous cell carcinoma of the head and neck presents with a biopsy proven metastatic cervical lymph node without an identifiable primary tumor site in approximately 2% to 4% of all cases.^{1–5} To identify the primary tumor, the typical diagnostic workup consists of a thorough physical examination, flexible endoscopy, and radiological imaging including positron emission tomography (PET)/CT. Surgical workup includes panendoscopy and directed biopsies of nasopharynx, oropharynx, and hypo-pharynx with the patient under

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general anesthesia. In spite of these seemingly comprehensive diagnostic tools, the primary tumor location in more than 40% of these cases remains unknown.^{5–9} As a result, patients with true carcinoma of unknown primary (CUP) undergo extensive head and neck irradiation and chemotherapy.^{10–13}

Recently, transoral laser microsurgery was found to be an effective approach in identification of CUP origin.^{14–17} Visual examination of the oropharynx under 3D magnification helps to identify malignant, vascular, and mucosal changes. Transoral tonsillectomy and lingual tonsillectomy with frozen analysis is a valuable diagnostic procedure in cases with no identifiable mucosal abnormality.^{14–20}

The purpose of this study was to analyze the feasibility of using transoral robotic surgery (TORS) to identify and remove the primary tumor in CUP cases and help to decrease the morbidity and mortality associated with adjuvant radiation or chemoradiation treatment.

MATERIALS AND METHODS

Among 181 patients who underwent TORS between April 2008 and May 2012 under an institutional review board–approved clinical TORS trial, 22 were found to have CUP.

The presenting symptom was a neck mass, which was biopsy proven to be squamous cell carcinoma metastatic to the cervical lymph nodes. A detailed physical examination including flexible laryngopharyngoscopy and radiographic imaging failed to demonstrate the primary tumor site. In an attempt to identify the primary site, all patients underwent PET/CT imaging before surgery. Panendoscopy, directed biopsies, TORS, and neck dissection were all performed with the patient under general anesthesia during the same surgical session.

First, panendoscopy including direct laryngoscopy, bronchoscopy, and esophagoscopy with biopsy of suspicious sites, if detected, were completed and sent for frozen section analysis. The robotic portion of the procedure was only initiated after completion of panendoscopy. If a site was identified with frozen section or highly suspicious PET/CT, panendoscopy, or robotic examination, complete primary tumor removal with TORS was planned. Multiple blind biopsies from the nasopharynx, pyriform sinuses, and base of the tongue were performed only if the primary site was still not pathologically confirmed after TORS resections were completed (Figure 1). Base of tongue sampling was achieved with TORS lingual tonsillectomy if the lingual tonsils were prominent. In case of nonprominent lingual tonsils, base of tongue lymphoid aggregates were removed as the inferior extent of the TORS palatine tonsillectomy specimen (Figure 2). These directed biopsy specimens were all sent for permanent pathologic analysis. Contralateral regular tonsillectomy was routinely performed in all patients.

TORS portion of the procedures has always been started after completion of panendoscopy and getting the frozen section result if submitted. The da Vinci Surgical System Model S or SI (Intuitive Surgical, Sunnyvale, CA) was positioned to the patient's right side. A Crowe–Davis mouth gag (Storz, Heidelberg, Germany) maintained tongue retraction and optimal palatine tonsil visualization. Exposure for lingual tonsillectomy was established with a Feyh–Kastenbauer (FK) retractor (Gyrus ACMI, Southborough, MA). An 11 mm Ø 3D

robotic camera together with a 5 mm Maryland dissector and a 5 mm spatula tip monopolar cautery were the routine robotic tools used. A 30' camera was preferred for lingual tonsillectomy. An assistant surgeon was available for smoke and blood evacuation and also tissue retraction while the surgeon was performing the procedure.

After completion of the robotic part of the procedure, the patient was draped and prepared for neck dissection. Bilateral neck dissection was performed in only 4 patients who showed clinical or radiologic evidence of positive contralateral lymph nodes. All other neck dissections were unilateral. Only 1 patient with a negative PET/CT scan after excisional lymph node biopsy at an outside facility rejected further neck dissection.

RESULTS

Nineteen male and 3 female patients with a median age of 56.6 years (range, 36–71 years) underwent TORS together with panendoscopy and neck dissection for CUP. Fifteen of 22 patients (68%) were smokers. Nodal stage at presentation was N2 in 16 (72.7%), N3 in 4 (18.2%), and N1 in 2 (9.1%).

The primary tumor site was identified as palatine tonsil (59.1%) and tongue base (18.1%) in 17 of 22 patients. In 5 patients (22.7%), the primary tumor location could not be identified. A majority of the patients had stage IV (90.9%) disease. Extracapsular spread was positive in 9 patients (40.9%). Human papillomavirus (HPV) and p16 positivity were 80% and 95%, respectively. HPV status was determined by in situ hybridization laboratory techniques. Bilateral primary tumors were found in 3 patients (17.6%; Table 1). Two patients had disease that involved the bilateral palatine tonsils and 1 patient's primary tumor was located in the base of tongue with multifocal involvement. All 3 patients were p16(+) but only the base of tongue primary and one of the bilateral palatine tonsil cases in this subset were HPV positive.

PET/CT was performed in all patients, but revealed the primary tumor location in only 9 (40.9%). The false-positive rate of PET/CT was 18.2%. PET/CT directed panendoscopy and directed biopsies helped to reveal the primary tumor site in 12 patients (54.5%).

Transoral robotic ipsilateral radical tonsillectomy and ipsilateral lingual tonsillectomy with base of tongue resection diagnosed and excised the primary tumor in 10 of 11 patients whose primary site was detected with highly suspicious PET/CT results, panendoscopy examinations, positive frozen sections from directed biopsies, and/or robotic examination. Two patients with a history of palatine tonsillectomy underwent lingual tonsillectomy only. Other patients underwent bilateral transoral robotic tonsillectomy with lingual tonsillectomy, which led to concurrent diagnosis and treatment in 7 of 9 patients (Table 2). Overall, utilizing all available diagnostic tools, including TORS resection, revealed the primary tumor site in 17 of 22 patients (77.3%). Of these 17, 13 patients (76.5%) had their primary tumors removed with negative surgical margins. Mean TORS operative and set up times were 28.5 minutes and 22.3 minutes, respectively. Bilateral neck dissection was performed for 4 patients with clinical or radiologic evidence of positive contralateral lymph nodes.

All patients tolerated an oral diet within the first 24 hours after surgery and avoided both tracheotomy and percutaneous endoscopic gastrostomy placement. Adjuvant radiotherapy was necessary for all patients (100%) but chemotherapy was avoided in 13 patients (59.1%; Table 3).

DISCUSSION

Management of head and neck cancer widely depends on the stage, grade, extension, and primary site of the tumor. Treatment recommendations regarding the management of CUP vary between institutions. Generally, the primary aim is to identify the primary tumor site and proceed according to the guidelines of occult primary tumors.^{5,8} However, because of difficulty of visualization, anatomic complexity, and the possibility of submucosal cancer, identification of the primary tumor can be challenging.

Despite the availability of several different diagnostic modalities, there is no 100% sensitive instrument for primary tumor site identification.⁶⁻¹³ Panendoscopy of the upper esophagus, trachea, bronchi, laryngopharynx, and nasopharynx with the patient under general anesthesia and directed biopsies of the clinically and radiologically suspected sites is often the diagnostic surgical method.^{10-14,20} However, the primary tumor site identification rate of this technique alone is only 17% to 40%.⁵⁻¹³ Preoperative PET/CT scan has a higher tumor site identification rate (44.2%) when compared to other radiological strategies; however, it has a false-positive rate of 28%. Treatment planning based on a PET/CT without pathologic confirmation is not recommended, because treatment could be directed toward a false-positive site, rather than the entire upper aerodigestive tract. This in turn causes undertreatment of the actual primary disease site.⁵⁻¹⁹ The highest rate of sensitivity among these approaches is achieved with the combination of PET/CT, panendoscopy, and directed biopsies, which is still reported to be no more than 59.6%.

Recently, Karni et al¹⁴ compared transoral laser micro-surgery with traditional rigid panendoscopic examination with directed biopsies for primary tumor site detection in cases of CUP. Retrospective analysis of 2 groups with 2 different diagnostic modalities was performed. In the transoral laser microsurgery group, mucosal surfaces were examined carefully under the microscope. In cases without a suspicious mucosal abnormality, diagnostic tonsillectomy and lingual tonsillectomy with frozen analysis were performed. The primary tumor identification rate was found to be 94% with transoral laser microsurgery compared to 25% in the panendoscopy group. Abuzeid et al¹⁷ reported a case of transoral robotic excisional tongue base biopsy of a patient with CUP. They successfully detected the primary tumor site, but their definitive treatment of choice was radiation therapy.

In our series, the overall primary site identification rate utilizing TORS was found to be 77.3%. In comparison to our previous published results, which yielded a sensitivity of 59.6% using a combination of panendoscopy and PET/CT, robotic methods improved our diagnostic ability by nearly 18%. The da Vinci robot was found to be a significantly useful tool for both detection of the primary tumor site and definitive treatment.²⁰ With its magnified 3D robotic camera and robotic instruments, it allowed for detailed examination of all mucosal surfaces including traditionally difficult to access anatomic areas. The

unencumbered view offered by the robot's 3D camera offers the surgeon a view of suspected sites superior to the naked eye and simple loupe magnification. Diagnosis by sampling suspected primary sites and definitive treatment with complete surgical excision was accomplished during the same surgical session 76.5% of the time. Detection and complete primary tumor removal with TORS not only focused the adjuvant treatment regimen but also deintensified it by decreasing the radiotherapy dose to the entire upper aerodigestive tract and avoiding adjuvant chemotherapy. Diagnostic palatine tonsillectomy and lingual tonsillectomy evaluation was achieved without difficulty while minimizing damage to surrounding mucosal surfaces with adequate hemostasis using the monopolar cautery arm within a relatively brief operative time span. Both diagnosis and definitive surgical resection of primary tumor site together with neck dissection were accomplished concurrently within the same surgical session.

CONCLUSION

TORS is a useful tool in both diagnosis and treatment of CUP. As reflected in the results from our study, it might effectively increase the diagnostic power when combined with PET/CT, panendoscopy, and directed biopsies.

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FIGURE 1.
Intraoperative decision-making algorithm for cancer of unknown primary (CUP) treated with transoral robotic surgery (TORS).

FIGURE 2.

Transoral robotic radical tonsillectomy and ipsilateral lingual tonsillectomy. (A) Surgery started as routine transoral radical tonsillectomy. (B) Resection is extended to include the ipsilateral lingual tonsil. (C) Excision is completed. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 1

Pathological findings.

Variable	No. of patients (%)
Overall stage (<i>n</i> = 22)	
I-II	0/22 (0)
III	2/22 (9.1)
IV	20/22 (90.9)
HPV status (<i>n</i> = 20)	
Positive	16 (80)
Negative	4 (20)
p16 status (<i>n</i> = 20)	
Positive	19 (95)
Negative	1 (5)
Bilaterality	
Palatine tonsil	2/3 (66.7)
Base of tongue	1/3 (33.3)
Surgical margin status (<i>n</i> = 22)	
Negative	18/22 (81.8)
Positive	4/22 (18.2)
ECS (<i>n</i> = 22)	
Present	9/22 (41)
Absent	13/22 (59)
Mean size of primary tumor	1.3 cm

Abbreviations: HPV, human papillomavirus; ECS, extracapsular spread.

TABLE 2

Type of diagnostic/therapeutic transoral robotic surgery.

Variable	Pathology positive	Pathology negative	Total no. of patients
Diagnostic lingual and palatine tonsillectomy	7	2	9
Diagnostic lingual tonsillectomy alone (surgical history of palatine tonsillectomy)	0	2	2
Radical tonsillectomy	7	1	8
Base of tongue resection	3	0	3
Total no. of patients	17	5	22

TABLE 3

Clinical outcomes.

Variable	No. of patients (%) (<i>n</i> = 22)
Neck dissection	
Unilateral	17/22 (77.2)
Bilateral	4/22 (18.2)
Excisional lymph node biopsy	1/22 (4.6)
Adjuvant therapy	
Radiation alone	13/22 (59.1)
Chemoradiation therapy	9/22 (40.9)