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Transoral Robotic Surgery and the Unknown Primary: A Cost-Effective Technique to Identify the Tumor

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Abstract

Objective—To evaluate the cost-effectiveness of transoral robotic surgery (TORS) for diagnosis and treatment of cervical unknown primary squamous cell carcinoma (CUP).

Study Design—Retrospective Review

Subjects and Methods—A retrospective chart review was performed on patients with new occult primary squamous cell carcinoma of the head and neck with non-diagnostic imaging and/or endoscopy who were treated with TORS at a tertiary hospital between 2009 and 2012. Direct costs (\$) were obtained from the hospital's billing system, and national data were used for inpatient hospital costs and physician fees. The proportion of tumors found in three strategies was used as effectiveness to calculate the incremental cost-effectiveness ratio.

Results—206 head and neck robotic cases were performed at our institution between December 2009 and December 2012. Three surgeons performed TORS on 22 patients for occult primary squamous cell carcinoma. The primary tumor was located in 19/22 (86.4%) patients. The incremental cost-effectiveness ratio for sequential and simultaneous EUA and TORS base of tongue resection was \$8619 and \$5774 per additional primary identified, respectively.

Conclusion—TORS is a cost-effective procedure to locate the primary tumor in patients with cervical lymph node metastases and no obvious source. Bilateral base of tongue resection should be considered as part of the exam under anesthesia for these patients, particularly if the palatine tonsils have already been removed.

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Introduction

Cervical metastasis from an unknown primary site, also known as the occult primary or cervical unknown primary (CUP), is relatively uncommon and accounts for less than 5% of head and neck cancers annually^{1,2}. Squamous cell carcinoma (SCC) accounts for roughly half to three-fourths of CUP histologies, and may be confirmed by fine needle aspiration (FNA) biopsy of the presenting cervical lymphadenopathy². When clinically unapparent, a primary site may be identified by endoscopy with either random biopsies or directed biopsies of concerning areas in conjunction with tonsillectomy or tonsillotomy. When physical exam and imaging findings are suggestive of an abnormality, directed biopsy identifies the primary site in approximately 2/3 of patients. However, the detection rate drops to approximately 30% in the absence of radiographic or physical findings^{2,3}. Overall, just over 50% of the primary tumors are located in patients who present with CUP².

Identification of the primary site is clinically and prognostically important. We previously reported a series of nine of ten patients in whom transoral robotic surgery (TORS) was used to locate the primary via base of tongue (BOT) resection⁴. Other groups have similarly reported success using transoral laser microsurgery (TLM) and TORS in this patient population, confirming its utility in identifying primary tumors^{5,6}. However, the use of the robotic technology has been criticized due to the added costs to the healthcare system^{7,8}. Definitive evidence regarding cost-effectiveness of robotic surgery overall is lacking in the literature, as the majority of cost-effective analyses on robotics have been performed in urologic and general surgery^{9,10}. The field of head and neck surgery has only recently begun to economically evaluate technology in healthcare. Richmon and colleagues recently published a cross-sectional study demonstrating hospital stay-related cost-savings in TORS compared to open surgery based on national cost data¹¹. De Almeida et al. have also made important early steps in quantifying health state utilities in TORS and chemoradiation for oropharyngeal cancer for future cost-utility analysis¹².

The purpose of this study is to evaluate the cost-effectiveness of transoral robotic surgery for localizing the cervical unknown primary based on our updated patient series.

Methods

With approval by the institutional review board, a retrospective review of all patients who underwent robotic surgery with diagnoses of squamous cell carcinoma and unknown primary at the University of Pittsburgh Medical Center was performed. Patients with physical exam and/or imaging findings suggestive of a primary tumor were excluded. All patients underwent flexible fiberoptic laryngoscopy in clinic, as well as panendoscopy prior to the TORS procedure, either at a previous setting or prior to docking of the robot.

TORS Surgical Procedure

Patients are induced with a general anesthetic and a small orotracheal tube. The surgeon then performs a direct laryngoscopy to examine the oropharynx, hypopharynx, and larynx for any suspicious lesions. If any suspicious lesions are noted, a frozen section is performed before

starting the robotic portion of the procedure, as an oncologic resection is performed if the tumor is identified.

The patient is positioned, the oropharynx exposed, the Da Vinci robot docked, and a lingual tonsillectomy is performed as previously described⁴. The surgeon then performs an examination of the specimen with the pathologist and requests a frozen section if any suspicious lesions are appreciated. If the tumor is localized by frozen section, additional margins are taken with the goal of complete resection and negative margins.

If tonsillectomy was performed, the retractor was repositioned with the tube over the midline tongue; the robot or a headlight and handheld electrocautery would be utilized for tonsillectomy based on surgeon preference.

Cost Analysis

A third-party payer cost-effectiveness analysis was performed to represent the schema depicted in Figure 1. Patients who underwent a transoral robotic bilateral base of tongue resection with or without simultaneous tonsillectomy with available billing information were identified out of the included patients. Patients who underwent traditional exam under anesthesia with tonsillectomy (EUA) within the same time period (2010–2012) were also selected; these patients were seen by surgeons who did not perform TORS, or were treated prior to the widespread adoption of TORS for CUP. Cost-to-charge ratios were used to calculate anesthesia, laboratory and pathology, pharmacy, radiology, and recovery costs (\$USD) from itemized charges captured by the hospital's electronic billing system. The operating room (OR) times, identified from the electronic medical record, were used to calculate OR costs the average operating room nurse and tech salary costs, based on the number of staff required for each case. Inpatient hospital costs were calculated using length of stay for each arm multiplied the calculated daily cost of hospitalization for oropharyngeal cancer (ICD-9 146) as retrieved from the U.S. Department of Health and Human Service Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (H-CUPnet) for the year 2011, the most recent data available¹³. The cost of one day of hospitalization was derived from H-CUPnet by dividing mean reported cost by mean reported length of stay for each oropharyngeal subsite. The mean cost per day over all oropharyngeal subsites (\$2657 USD) was then multiplied by length of stay to calculate Hospital Cost. Physician fees were obtained from the Centers for Medicare and Medicaid Services website (www.cms.gov)¹⁴ for 2011 using non-facility values. Nasopharyngoscopy is not included in cost analysis because it is routinely performed in clinic.

Incremental costs and effectiveness were used to calculate the incremental cost-effectiveness ratio (ICER) for traditional EUA/tonsillectomy with subsequent TORS base of tongue resection and for combined TORS base of tongue resection with tonsillectomy.

Results

Two hundred and six head and neck robotic cases were performed at our institution between December 2009 and December 2012. Twenty-eight patients with diagnoses of “unknown primary” were identified. Three of these patients were excluded due to tumors found on

physical exam in the office or by imaging, two because they represented regional recurrences from previously treated head and neck cancers, and one patient was diagnosed by FNA biopsy with a metastatic liver carcinoma. Twenty-two patients met study criteria.

Patient demographics are listed in Table 1. The mean age was 55.1 years (range 43–75), three patients were female, and all patients were Caucasian. A history of tobacco use was reported in 54.5%. All patients were reported alive at last follow-up (mean 19.9 months, range 3–32 months).

Table 2 lists procedures performed. 11 patients had bilateral base of tongue resection alone, 3 had unilateral base of tongue resection, 6 had simultaneous tonsillectomy and bilateral base of tongue resection, and 2 had simultaneous bilateral tonsillectomy and unilateral base of tongue resection. Three patients had simultaneous neck dissections. Intraoperative frozen section was performed in 4 patients at the time of laryngoscopy; this localized the tumor in the right base of tongue in one patient who had previously undergone tonsillectomy and direct laryngoscopy with biopsy.

No patients required gastrostomy or tracheotomy. There was one complication: a patient who underwent base of tongue resection was readmitted on postoperative day 8 for severe pain and dehydration. A nasogastric tube was placed temporarily and he was discharged four days later on an oral diet.

Table 3 lists pathological characteristics of the tumors identified. Overall, the primary tumor was localized in 19/22 patients (86.4%), and negative margins were noted on permanent pathology in 10 of 19 patients in whom the tumor was found (52.6%). Only one of these patients had a frozen section that identified the tumor intraoperatively; in the remainder the tumor was found with negative margins by permanent pathology. In 21/22 patients, HPV and/or p16 testing was available. In 17 patients p16 and HPV were positive; in 1 additional patient p16 was positive and HPV testing was unavailable. In 2 patients p16 was positive and HPV was negative, and in 1 HPV and p16 were negative.

Two patients were treated with TORS, neck dissection, and observation. Two patients went on to have postoperative radiation, three to radiation and targeted therapy, and fifteen were treated with combined chemoradiation.

Cost-Effectiveness Analysis

Eight patients underwent standard EUA/tonsillectomy within the timeframe of interest. Of the 11 patients who underwent TORS base of tongue resection, 1 patient was excluded from cost analysis because his surgery was performed at a different hospital, and itemized cost information was not available. One patient in the TORS BOT group had no reported Recovery cost; this selected value was excluded from analysis so the average value would not be falsely low. One patient of six who underwent simultaneous EUA/TORS was excluded from cost analysis because a simultaneous neck dissection was performed.

Table 4 lists the average direct costs, hospital costs, and total costs for standard EUA/tonsillectomy, TORS BOT resection, and simultaneous EUA/TORS. Itemized direct cost information is available in Supplemental Table 1. Length of stay for EUA is 0, as it is an

outpatient procedure. All patients undergoing TORS BOT resection stayed for one postoperative day. Two of five patients in the simultaneous EUA/TORS group had LOS 2 days, and the remainder had LOS 1 day; the average for the group is 1.4 days.

Table 5 lists the Current Procedural Terminology (CPT) codes and physician fees for each procedure, followed by the costs for each treatment arm. The overall physician cost for each treatment arm was calculated according to standard billing practices, starting with the procedure with highest reimbursement, followed by one-half the cost additional procedures when performed simultaneously.

The previously reported 30% identification rate was used for the EUA/Tonsillectomy group³. The effective identification rate for the sequential EUA/TORS BOT resection group was calculated by adding the EUA/Tonsillectomy identification rate (30%) to the percent identified by TORS BOT resection in the remaining 70% of patients (70% not found $\times$ 9/11 found by TORS BOT resection, 87%). In the 6 patients who underwent simultaneous EUA/TORS, 100% of tumors were localized.

Table 6 lists the costs and percent tumor localization (effectiveness) for each of the three arms depicted in Figure 1. The incremental cost-effectiveness ratio was \$8619 per additional primary identified for sequential EUA and TORS base of tongue resection, and \$5774 per additional primary identified for simultaneous EUA and TORS base of tongue resection. Due to the small number of patients on which the simultaneous EUA/TORS strategy proportion identified was based, a one-way sensitivity analysis was performed varying the proportion identified (Table 7, Figure 2). According to the principle of extended dominance, simultaneous EUA/TORS would be the dominant strategy with in incremental effectiveness of 0.087 or greater, corresponding to a proportion identified of 0.957 for the group¹⁵.

Discussion

This is the first study investigate the cost-effectiveness of TORS in unknown primary. The study is performed from the third-party payer perspective, which does not include fixed hospital costs. At our institution, a robotic surgery program is already established; a hospital perspective including the cost of purchase and amortization of the Da Vinci robot would need to be adopted to represent the cost of implementing a new robotic surgery program¹⁶.

We report the cost-effectiveness in terms of the incremental cost-effective ratio (ICER), with proportion tumor localization as effectiveness; in contrast to the investigation by Richmon et al.¹¹, there is no open group for comparison, only the option to treat nonoperatively if TORS is not performed. Overall, the incremental cost-effectiveness ratio for TORS after EUA is favorable. In cost-utility analyses, there is a rule of thumb that a cost of \$50,000 to \$100,000 per quality-adjusted life year gained is considered acceptable¹⁷. Whether society would be willing to pay \$8,619 or \$5774 for each primary tumor detected is uncertain.

However, there are some clear benefits of locating the primary tumors, such as the potential to minimize radiation to other sites if the tumor is detected, and also to obviate radiation in selected cases when a negative margin resection is achieved and the neck is addressed surgically. Although the majority of the patients in this study were treated with three

modalities, two patients were treated with a single modality, and five additional patients were spared chemotherapy. Also, the proportion of patients with CUP who are HPV/p16+ would be expected to increase commensurately with that of oropharyngeal cancer. It is likely that many of these patients will avoid chemotherapy in the future, as early studies have demonstrated that its added benefit may be limited^{18,19}. There is some retrospective evidence that identifying the primary tumor is associated with improved survival. Haas et al. reported 100% 3-year survival in patients whose oropharyngeal primary was located (N=8) versus 58.8% in those with a true “occult primary” (N=34)²⁰. In a report by Karni et al. investigating transoral laser microsurgery (TLM) as a technique to locate the primary tumor, Kaplan-Meier survival outcomes were 100% in the “found” group versus 44% in the “not found” group²¹. However, strong inferences cannot be drawn from these studies due to the small sample sizes, disproportionate number of patients with N3 disease in the “not found” group in the former study, and failure to report and/or control for stage in the latter. Others have reported that finding the primary site does not change prognosis²². In our small cohort, all patients were alive at last follow-up, and conclusions about survival benefit and outcomes cannot be drawn. Further study is needed to quantify the incremental costs of this procedure to the health utility gained by this approach.

The overall localization rate for all patients in this study (86.4%) compares favorably with other published studies of transoral surgery for cervical unknown primary. Karni et al. compared transoral laser microsurgery (TLM) with traditional EUA, finding a 94% detection rate compared to 25% in 30 patients²¹. Similarly, Nagel and colleagues recently published an 86% detection rate in the largest reported series of 36 TLM patients using their reported algorithm of directed biopsies, frozen section, and lingual tonsillectomy⁵.

At our institution TORS is used for oropharyngeal cancer, rather than TLM. After overcoming the learning curve, we find that setup and docking time are very minimal, and the wide exposure afforded by the retractor allows complete resection of the base of tongue and tonsils with minimal repositioning. The use of the Da Vinci robot in CUP was first introduced by Abuzeid et al. in a case report in 2011²³. Shortly thereafter, this group reported a 90% localization rate using base of tongue resection in 10 patients who had failed prior EUA⁴. Similarly, Durmus and colleagues published a series of 22 patients who underwent TORS with 77% tumor identification⁶. Surgeon preference should guide technique for transoral surgery. Overall, the existing literature has supported the success of transoral surgery in CUP.

Our expanded patient series includes only those who meet the strictest definition of CUP; patients who had suggestive physical exam or imaging findings were excluded. Many of the patients had undergone previous tonsillectomy, either in childhood or during prior EUA; hence these patients went directly to TORS base of tongue resection. PET/CT has been studied as a means to identify the primary tumor in CUP. However, a recent meta-analysis of retrospective studies yielded a detection rate of only 37%²⁴. In our study, we excluded patients with definitively localizing imaging. Only one patient had some increased activity on PET/CT where the tumor was ultimately found.

Initially, patients in this series underwent base of tongue resection and/or tonsillectomy without frozen section, as the goal of surgery was to localize the tumor only. However, our treatment algorithm evolved with the goal of complete tumor resection, as described by other groups, and the surgeon now evaluates the specimen with the pathologist in an attempt to re-resect margins at the time of TORS when possible. Due to the small tumor size (1 cm) and the cryptic structure of the lingual tonsils, localization by frozen section is not always possible. Therefore, our group plans robotic re-resection at the time of delayed neck dissection in patients who are being treated surgically. Blind biopsy on direct laryngoscopy at the time of TORS was positive in one patient; this patient had undergone previous EUA, which was negative.

There were no postoperative hemorrhages or major complications. One patient in the series who had TORS BOT resection required readmission for dehydration. Because this is within the acceptable complication rate for TORS, his readmission was not factored into this cost-effectiveness analysis.

The limitations of this study include a small sample size and its retrospective nature. Additionally, the societal perspective, rather than the third-party payer perspective, is the ideal for a true cost-effectiveness study. However, it was not feasible to collect the necessary data for the societal perspective in this retrospective analysis. Finally, the lack of health-related quality of life outcomes prevented cost-utility analysis, and therefore the true impact of our interventions.

The simultaneous EUA/TORS treatment strategy is associated with lower direct hospital costs and physician fees compared to the sequential strategy. However, two of five patients who underwent the procedure required two inpatient days for pain control and inability to tolerate PO, which resulted in increased overall cost for the strategy. It is likely that there is a significant increase in pain associated with simultaneous base of resection and tonsillectomy, and there is a concern for the late development of circumferential stenosis, especially after radiation or concurrent chemoradiation. Additionally, the 100% tumor localization in the group is likely artificially high due to the low sample size, and the actual identification rate is likely somewhere between the overall rate of 86.4% in this study and the highest published rate of 94%²¹, which would lower the ICER. Due to the increased potential for complications and the small potential increase in tumor identification, we advocate for delayed TORS if the tumor is not identified at the time of EUA/tonsillectomy.

Conclusion

TORS is a cost-effective technique for tumor localization and resection for patients with squamous cell carcinoma cervical unknown primary. In a small series of patients, performing TORS base of tongue resection in patients who fail exam under anesthesia with tonsillectomy was associated with decreased length of stay and lower overall cost than simultaneous EUA and TORS base of tongue resection. A randomized clinical trial is necessary to determine the ultimate impact of finding the primary site on survival and quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Treatment strategies for Cervical Unknown Primary Carcinoma

Figure 2.

One-way sensitivity analysis of incremental cost-effectiveness ratio for the simultaneous EUA/TORS strategy, varying the proportion identified.

Table 1

Patient Characteristics

Age (years, range)		55 (43–75)
Sex		
Male	19/22	86.4%
Female	3/22	13.6%
History of Tobacco Use		
Yes	12/22	54.5%
No	10/22	45.5%
cN Stage		
N1	9/22	40.9%
N2	11/22	50.0%
N3	2/22	9.1%
Prior Endoscopy		
Yes	9/22	40.9%
No	13/22	59.1%
Imaging		
PET/CT	19/22	86.4%
CT Neck	3/22	13.6%

Table 2

Procedures

	Number (n)	Primarys Identified, # (%)
Unilateral Base of tongue Resection	3	3 (100)
Bilateral Tonsillectomy with Unilateral Base of Tongue Resection, Neck Dissection *	2	1 (50)
Bilateral Base of Tongue Resection	11	9 (81.8)
Bilateral Tonsillectomy and Base of Tongue Resection	5	5 (100)
Bilateral Tonsillectomy and Base of Tongue Resection, Neck Dissection	1	1 (100)

* One patient whose primary was not identified went on to have a contralateral base of tongue resection at a later time

Table 3

Pathological Characteristics

Variable Found	Result	
Yes	19/22	86.4%
No	3/22	13.6%
Subsite		
Tonsil	3/22	13.6%
Tongue Base	16/22	72.7%
Laterality		
Ipsilateral	18/22	81.8%
Contralateral	1/22	4.5%
Tumor Size		
cm (SD)	1.03	(0.66)
HPV/p16		
Positive	20 [*] /21	90.5%
Negative	1/21	4.8%
Margin		
Negative	10/19	52.6%
Positive	9/19	47.4%
ECS		
Positive	3/9	33.3%
Negative	6/9	66.7%

* 2 patients were HPV- and p16+. HPV/p16 was unavailable in 1 patient

Table 4

	OR Minutes (SD)	Surgical Minutes (SD)	Total Direct Costs (SD)	Length of Stay	Inpatient Costs ^{1,4}	Total Hospital Costs
EU/A/Tonsillectomy (n = 8)	77 (23.9)	52 (19.9)	\$832 (133)	0	\$-	\$832
TORS BOT Resection (n = 10)	157 (38.2)	111 (35.7)	\$1789 (361)	1	\$2,657	\$4,446
Simultaneous EU/A/TORS (n = 5)	160 (36.3)	113 (35.8)	\$2169 (565)	1.4	\$3,720	\$5,889

Table 5

Procedure	CPT	Cost (\$)¹⁵
Lingual Tonsillectomy	42870	609.01
Esophagoscopy with Biopsy	43202	301.44
Tonsillectomy >12 years old	42826	259.94
Direct Laryngoscopy with Biopsy	31535	192.91
Treatment Arm Costs		
EUA		527.87
Sequential EUA/TORS		954.18
Simultaneous EUA/TORS		986.16

Table 6

	Hospital Costs (\$)	Physician Costs (\$)	Total Costs (\$)	Effectiveness (Proportion Identified)	Incremental Cost (\$)	Incremental Effectiveness (%)	ICER
EUA/Tonsillectomy	832	528	1360	0.3	0	0.00	0
Sequential EUA/TORS	5318	954	6272	0.87	4913	0.57	8619
Simultaneous EUA/TORS	6037	986	7023	1	751	0.13	5774

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Table 7
One-way ensitivity analysis for ICER of Simultaneous EUA/TORS varying proportion identified

Total Costs (\$USD)	7023	7023	7023	7023	7023
Incremental Cost (\$USD)	751	751	751	751	751
Proportion Identified	0.9	0.925	0.95	0.975	1
Incremental Effectiveness	0.03	0.055	0.08	0.105	0.13
Incremental Cost-Effectiveness Ratio	25033	13655	9388	7152	5777