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Transoral Robotic versus Open Surgical Approaches to Oropharyngeal Squamous Cell Carcinoma by Human Papillomavirus Status

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Abstract

Objectives. (1) Investigate oncologic survival outcomes and (2) analyze the impact of human papillomavirus status on prognosis in patients with oropharyngeal squamous cell carcinoma treated with transoral robotic versus open surgery.

Study Design. Retrospective cohort study.

Setting. Tertiary care referral center, University of Alabama at Birmingham Hospital.

Subjects. One hundred thirty total (65 per treatment arm) with primary oropharyngeal squamous cell carcinoma (OPSCC).

Methods. Patients treated for primary oropharyngeal squamous cell carcinoma with either transoral robotic (TORS) or open surgery plus standard of care adjuvant therapy between October 2004 and March 2012 were matched based on TNM staging before a retrospective chart review was performed. Carcinoma tissue was stained both prospectively and retrospectively with CINtec p16-INK4a kits for surrogate human papillomavirus typing. Recurrence-free survival was used to evaluate the impact of human papillomavirus tumor status and method of surgical intervention on prognosis.

Results. As a whole, patients treated with transoral robotic surgery survived more frequently (94%, 91%, 89% at 1, 2, 3 years, respectively) than those treated with open surgery (85%, 75%, 73% at 1, 2, 3 years, correspondingly) ($P = .035$). The subgroup of patients with human papillomavirus-negative malignancies treated with open surgery survived without recurrence less frequently at 1, 2, and 3 year rates of 58%, 25%, 25%, respectively ($P < .01$).

Conclusion. These retrospective data suggest that oncologic outcomes are not being sacrificed when patients with OPSCC are treated with TORS instead of open surgery regardless of tumor human papillomavirus immunohistochemical staining.

Keywords

transoral, robotic, surgery, TORS, oropharynx, carcinoma, human papillomavirus, HPV, survival, p16, p16-INK4a

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Introduction

Transoral robotic surgery (TORS) is rapidly emerging as a safe, feasible, and efficient alternative to both open surgery and combined chemoradiation for use in treating primary oropharyngeal squamous cell carcinoma (OPSCC). The Food and Drug Administration has approved the use of Intuitive Surgical, Inc's (Sunnyvale, California) da Vinci surgical system for ''transoral otolaryngology surgical procedures restricted to benign and malignant tumors classified T1 and T2,'' and more broad approval is likely to come in the future.[1,2] The timing of this advancement could not have been better, as the incidence of OPSCC is rising and the oncologic outlook for patients with OPSCC is improving.[3]

The National Cancer Institute estimated that approximately 40,250 individuals in the United States would be diagnosed with cancer of the oral cavity and pharynx in 2012. Caucasian men continue to dominate this population's

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constituency, and the majority of patients (70.2%) are diagnosed between 55 and 84 years of age.[3]

The trends in OPSCC can be explained by a dramatic increase in the number of human papilloma virus (HPV)-associated cases, particularly of the tongue base and palatine tonsil, that is outpacing a slight decline in cases tied to alcohol and tobacco-mediated carcinogenesis, the traditional etiologic agents. The Centers for Disease Control and Prevention cite an OPSCC HPV positivity rate of 63%.[4] Recent reports reveal high rates of HPV positivity via HPV real time polymerase chain reaction (rtPCR), HPV in-situ hybridization (ISH), and/or p16-INK4a (p16) immunohistochemistry (IHC) ranging from 72% to 90%.[5-8]

Patients with carcinoma of the oral cavity and pharynx traditionally had a relatively grim prognosis, with a 5-year overall survival rate of 61.5%.[3] Reports for patients with OPSCC testing positive for HPV and treated with transoral surgery showed improved survival with rates between 82% and 92%.[6,8-10] To our knowledge, recurrence-free survival and oncologic outcomes following primary intervention with TORS have yet to be definitively compared in a case control study to open surgery while taking HPV status into account. The purpose of this study is to evaluate the impact of HPV status for patients treated with either TORS or open surgery.

Materials and Methods

Patient Selection

Between April 2007 and September 2011, 65 patients with OPSCC were treated with primary TORS and standard of care adjuvant therapy based on pathologic findings and met inclusion criteria. These cases were retrospectively matched based on TNM staging with 65 control patients treated for OPSCC with open surgery and similar adjuvant therapy at the University of Alabama at Birmingham (UAB) Hospital between October 2004 and August 2011. T staging was valued over N staging in this matching process. Informed consent was gained from all TORS patients for the use of clinical information, and pathology informed consent was waived in order to retrospectively retrieve and stain cancer tissue for p16-INK4a in patients who did not have such staining done as part of their peri-operative pathologic evaluation. Informed consent for patients treated with open surgery was retrospectively waived. The UAB Institutional Review Board approved this project and its amendments.

Exclusion Criteria and Blinding

Patients were excluded if they refused postoperative adjuvant therapy when clearly indicated. Patients were also excluded from analysis if they failed matching, had an unknown primary carcinoma site, or had a non-oropharyngeal primary cancer. If TORS was abandoned intraoperatively in favor of open surgery for any reason, the case was also excluded. No patients were excluded based on race, gender, age, or social history. Researchers were blinded to both the patient's outcome and their HPV status when initially matching TORS cases to open surgical controls.

Treatment Categorization

Intuitive Surgical, Inc's (Sunnyvale, California) da Vinci Robot was used to gain transoral access to cancers in the TORS group. Open surgical approaches used in the control group included transcervical, transfacial, transmandibular, and transoral (without the use of a robot). Free-flap reconstruction was sometimes necessary following open surgery. Two surgeons performed all TORS procedures (JSM, WRC).

Data Collection

Demographic, pathologic, treatment, social, follow-up, and survival data were used in this comparison. Demographic data collected included age, gender, and race. Race was defined by the examining physician(s) and was recorded to ensure congruous patient populations. Oropharyngeal cancers were defined as originating from the oropharyngeal wall, base of tongue, palatine tonsil, and soft palate. Pathologic data collected for analysis included disease location, staging, nodal status, extracapsular spread, perineural invasion, and lymphovascular extension. Tumor p16 staining results were identified and recorded when available in patients' pathology reports as well. Cancers were staged using the American Joint Committee on Cancer's TNM staging system. Treatment data used in addition to type of primary surgery included adjuvant chemotherapy, radiation therapy, and cervical lymph node (CLN) dissection. Margin data were collected and classified as positive, close (<5 mm), or negative. Social data, particularly tobacco use rates, were also collected for analysis. Total follow-up span, last known disease status, and mortality data were used to construct Kaplan-Meier survival curves of recurrence-free survival. Patients lost to follow-up, defined as failing to visit the clinic within 2 times the recommended follow-up time frame or 18 months, were screened through the Social Security Death Index, CDC Death Index, Google online searches, and obituary searches to screen for undocumented mortality.

p16-INK4a Staining

Paraffin-embedded OPSCC tissues confirmed to contain adequate carcinoma tissue were stained to determine the p16 status of patients' cancers. CINtec Histology p16-INK4a manual staining kits were used. Following hydration, peroxidase blocking, epitope retrieval, primary antibody application, secondary antibody application, visualization, dehydration, and paraffin embedding, tissues were microscopically examined to determine p16 positivity or negativity. HPV positivity was defined as strong intra-nuclear and intra-cytoplasmic p16 expression within 75% or greater OPSCC cells. This process was performed in accordance with guidelines provided by CINtec Histology. One pathologist reviewed all retrospective p16 immunohistochemical slides (MBG).

Analysis

Fisher exact testing was used to compare dichotomous variables (eg, yes/no) when at least 1 of the control (open surgery, non-TORS) variables had a frequency of less than or

Table 1. Patient Demographics and Treatment.

	Transoral Robotic (n = 65)	Open (n = 65)	*P* Value
Age, mean (SD), yrs	59 (11)	58 (10)	.98[a]
Gender, n (%)			
Male	52 (80)	51 (78)	.76[b]
Female	13 (20)	14 (22)	
Race, n (%)			
White	50 (77)	56 (86)	.23[b]
Black	2 (3)	3 (5)	.34[c]
Other	1 (1)	1 (1)	>.99[c]
Unknown	12 (18)	5 (8)	
Disease location, n (%)			
Tonsil	38 (58)	43 (66)	
Tongue base	21 (32)	9 (14)	<.01[b]
Oropharyngeal wall	6 (9)	12 (18)	
Soft palate	0 (0)	1 (1)	
Tobacco use history			
Ever tobacco user, n (%), n of subjects	41 (66), 62	34 (64), 53	.08[b]
Tobacco user post-diagnosis, n (%), n of subjects	21 (35), 60	19 (37), 51	.18[b]
Pack year equivalents, mean (SD), yrs	34 (19)	45 (33)	.14[a]
Adjuvant therapy			
Radiation, n (%)	43 (66)	40 (62)	.44
Chemotherapy, n (%)	17 (26)	19 (29)	.56
CLN Dissection, n (%)	56 (86)	56 (86)	>.99

Abbreviation: CLN, cervical lymph node.
[a]Two-tailed *t* test assuming unequal variance.
[b]Chi-square analysis.
[c]Fisher exact analysis.

equal to 5. Chi-square testing was used when all control variable frequencies were greater than 5. T-tests with 2 tails assuming unequal variance were used in comparing numerical variables (eg, cumulative pack year smoking history). Kaplan-Meier regression curves were used to compare recurrence-free survival between the various treatment groups and subgroups. Long-term end-point survival estimates generated in our analyses were excluded for 2 reasons: (1) differences in follow-up duration between the 2 groups and (2) to avoid misleading readers by irresponsibly extrapolating data on relatively small cohorts.

Results

Demographic, disease subsite, social, and adjuvant therapy data are listed in **Table 1**. The average age, gender distribution, and race distribution of the both patient groups were equivalent. More tongue base lesions were resected in the TORS series (21 vs 9, $P < .01$); oropharyngeal wall and tonsillar carcinomas made up the difference in disease subsite localization within the control group. Smoking rates were similar between groups both before ($P = .08$) and after ($P = .18$) diagnosis, as were cumulative pack year equivalents of lifetime tobacco consumption among smokers ($P = .14$). A trend toward higher rates of tobacco use among patients treated with TORS is present in this data. Alcohol consumption was too inconsistently reported to evaluate. Rates of adjuvant chemotherapy and radiation therapy were indistinguishable.

Staging data are provided in **Table 2**. T staging, the primary variable used in matching, was completed without exception ($P > .99$). N stage and overall stage did not differ significantly between the 2 groups ($P = .26$). Overall, the total number of early (stages 1 and 2) and advanced (stages 3 and 4) stage cases included in each arm was equivalent.

Pathologic data are provided in **Table 3**. Margin status of the primary resection was similar between the 2 groups. Also, there was no difference noted in the incidence of cervical metastasis. Poor prognostic indicators (extracapsular spread, perineural invasion, lymphovascular invasion) were the same in both groups. A trend toward more positive lymph nodes was seen in the open group compared to the TORS group ($P = .07$). Carcinoma tissue from 81% and 79% of patients tested positive for HPV in the TORS group and open group, respectively.

Survival

Independent of HPV status, recurrence-free survival rates for the TORS and open surgical cohorts were 94%, 91%, and 89% and 85%, 75%, and 73% at 1-, 2-, and 3-year postoperative intervals, respectively ($P = .035$ by Breslow analysis) (**Figure 1**). For HPV-positive patients, no significant difference in survival

Table 2. Staging.

Staging Type, N (%)	Transoral Robotic (n = 65)	Open (n = 65)	*P* Value
T stage			
1	21 (32)	21 (32)	
2	36 (55)	36 (55)	>.99[a]
3	6 (9)	6 (9)	
4	2 (3)	2 (3)	—[b]
N stage			
0	14 (22)	14 (22)	
1	8 (12)	13 (20)	.23[a]
2a+b+c	42 (65)	36 (55)	
3	1 (2)	2 (3)	—[b]
Overall staging			
1	4 (6)	4 (6)	—[b]
2	10 (15)	10 (15)	
3	7 (11)	12 (18)	.26[a]
4a+b	44 (68)	39 (60)	

[a]Chi-square analysis.
[b]Row excluded in chi-square analysis (n ⩽ 5).

Table 3. Pathologic Data.

Parameter, N (%)	Transoral Robotic (n = 65)	Open (n = 65)	*P* Value
Positive margins	10 (15)	12 (18)	.52[a]
Close margins (<5 mm)	8 (12)	6 (9)	.39[a]
CLN carcinoma dissemination	51 (78)	51 (78)	>.99[a]
Extracapsular tumor spread	28 (58) (n = 48)	26 (55) (n = 47)	.65[a]
Perineural invasion	6 (9)	5 (8)	.50[b]
Lymphovascular invasion	5 (8)	5 (8)	.26[b]
N positive CLNs, average (SD)	2.1 (1.7)	3.2 (3.8)	.07[c]
HPV positivity (via p16 staining)	51 (81)	44 (79)	.29[a]

Abbreviation: CLN, cervical lymph node.
[a]Chi-square analysis.
[b]Fisher exact analysis.
[c]Two-tailed *t* test assuming unequal variance.

was seen for either surgical technique (98%, 94%, 91% vs 93%, 92%, 91%) (**Figure 2**). There was, however, a lower recurrence-free survival rate observed among the subgroup of HPV-negative patients treated with open surgery versus TORS (**Figure 3**). Available survival data for this subgroup was small (12 per group), limiting statistical analysis between these 2 groups. There were no early postoperative deaths, defined as occurring within 30 days of surgery, in either group.

Discussion

The purpose of this study was to assess the impact of HPV status on survival for patients treated with either TORS or open surgery followed by standard of care adjuvant treatment. The disease-free survival rates and incidence of HPV positivity in this study are similar to recent reports.[5-10]

Attempts to limit the selection bias between these 2 groups was made by including open surgeries performed prior to the introduction of TORS at the institution (2007). Matching the control group (open surgery) to the TORS group was primarily accomplished using T stage, which produced no significant differences in N stage or overall stage between the 2 groups.

It is interesting to note no difference in HPV positivity between the 2 groups (81% and 79%), suggesting that HPV status likely had an impact on survival in years past. When using multimodality treatment on patients positive for HPV, survival rates are excellent (over 90% 3-year survival).

On the other hand, patients testing negative for HPV portend a significantly worse survival compared to HPV-positive patients. This study identified a trend for improved survival in this subgroup when treated with TORS. With such a small number of patients treated in this group, it is not possible to explain this difference, which may be due to study design and some inherent

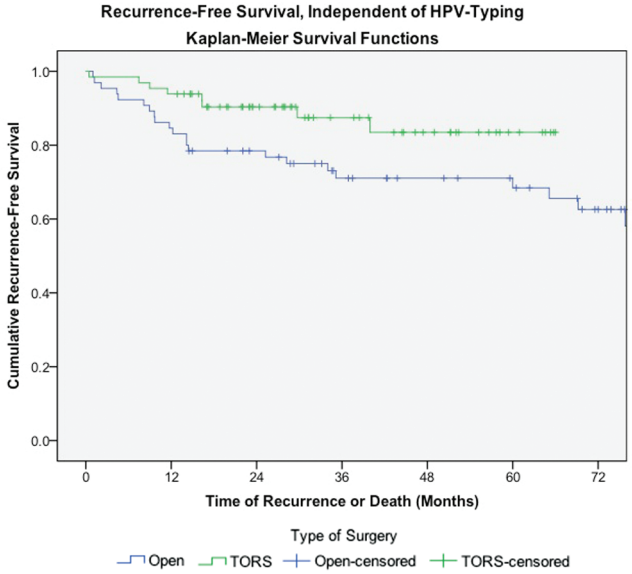

Figure 1. Recurrence-free survival, independent of histologic human papillomavirus typing. TORS, transoral robotic.

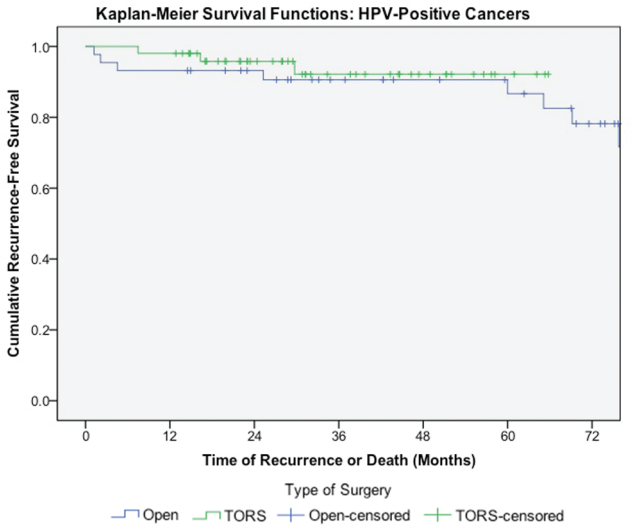

Figure 2. Recurrence-free survival among with patients human papillomavirus-positive malignancies of the oropharynx. TORS, transoral robotic.

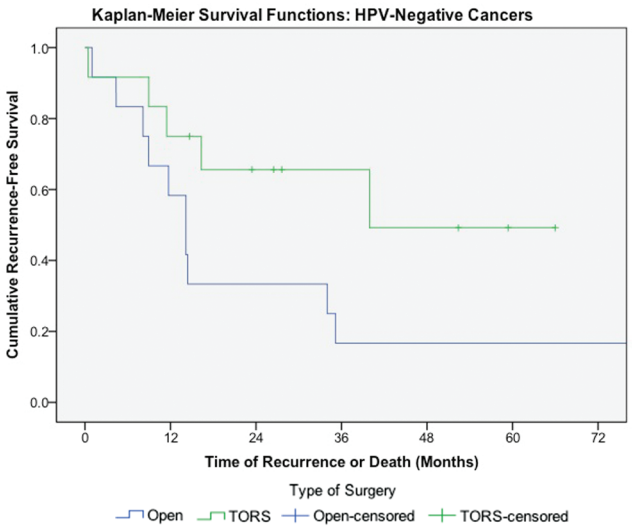

Figure 3. Recurrence-free survival among patients with carcinomas staining negative for human papillomavirus. TORS, transoral robotic.Figure 1, 2, and 3 Legend.

selection bias. No stark differences in the pathology data of the 2 HPV-negative groups point to any clear explanation of this difference. A larger evaluation is necessary.

Patients treated with traditional open surgery in our series tended to fare worse than those treated with TORS. This difference cannot be explained using differences in pathologic outcome parameters (eg, margin status, extracapsular spread, etc). It is possible that since TORS is a less morbid procedure, sparing patients the morbidity of a traditional open procedure affords survival benefit in and of itself. Although we do not have the data to examine this, it is also possible that patients treated with traditional open surgery more often have their adjuvant therapy delayed to allow adequate postsurgical healing time.

This study does confirm the possibility of treatment reduction plans for patients with OPSCC testing positive for HPV. Clinical trials are now underway to evaluate possible reductions in adjuvant chemotherapy and radiation therapy for these patients.[11-13]

Author Contributions

Samuel E. Ford, conception, design, data acquisition, analysis, interpretation, manuscript drafting, manuscript revision; **Margaret Brandwein-Gensler**, data acquisition, analysis, manuscript revising; **William R. Carroll**, data acquisition, manuscript revision; **Eben L. Rosenthal**, data acquisition, manuscript revision; **J. Scott Magnuson**, design, data acquisition, manuscript revision.

Disclosures

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