A POPULATION-LEVEL ASSESSMENT OF TRANSORAL SURGERY FOR OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Background: Transoral oral surgery, including robotic surgery (TORS) and endoscopic approaches, is an emerging treatment modality for oropharyngeal squamous cell carcinoma (OPSCC) that has demonstrated excellent oncologic and functional outcomes. The purpose of this study is to examine national patterns of care and short-term surgical outcomes among patients undergoing transoral for OPSCC.

Methods: Cross-sectional analysis of OPSCC patients undergoing primary transoral surgery in 2010-2011 was conducted using data from the National Cancer Database (NCDB). The NCDB is a large national cancer registry sponsored by the American College of Surgery Commission on Cancer (ACS-COC) and the American Cancer Society. Demographic, tumor and treatment characteristics, length of stay, surgical margin status, short-term complications, and postoperative mortality were evaluated.

Results: 700 patients undergoing primary transoral surgery for OPSCC were identified and included in the study cohort. The median age was 58 years (range 30 to 90), and the majority of patients were male (84%). 90% of patients were non-Hispanic White, 6% African American, 3% Hispanic, and 1% Asian. 57% of patients received treatment at academic medical centers, 29% at Community Cancer Centers, and 14% at Community treatment facilities. The majority of patients had primary tumors of the tonsil (77.4%), and a smaller proportion had tumors involving the base of tongue (18.6%) and pharyngeal wall (4%). AJCC (7th edition) Clinical T-stage distribution was as follows: 44% T1, 44% T2, 9% T3, and 3% T4.

56.9% of patients underwent TORS and 43.1% other forms of transoral endoscopic resection. Final surgical margins after resection were positive for carcinoma in 27.4% of all patients. On multivariable analysis, positive margin status was significantly associated with advanced T-stage (T2 vs. T1 adjusted OR 2.24 95% CI 1.32-3.81, p<0.05; T4 vs. T1 adjusted OR 4.2 95% CI 1.40-12.61, p<0.05) and with non-robotic endoscopic vs. TORS approach (adjusted OR 2.43 95% CI 1.60-3.69, p<0.001). Treatment in community cancer facilities vs. academic centers (adjusted OR 1.97 95% CI 1.29-2.99, p<0.05), and treatment in low case volume centers vs. high case volume centers (adjusted OR 2.40 95% CI 1.35-4.27, p<0.05) were also significantly associated with a higher risk of positive surgical margins after TOS. The mean length of hospitalization was 3.8 days (SD 7.5), the rate of unplanned 30-day readmission was 3.1%, and the 30-day postoperative mortality rate was 0.6%.

Conclusions: Transoral surgery is increasingly utilized across the United States, most commonly at academic medical centers and in patients with early-stage OPSCC. This population-level assessment demonstrates a low rate of unplanned hospital readmission rates and postoperative mortality associated with this treatment modality. A high rate of positive surgical margins was noted, particularly among patients with advanced T-stage, non-robotic transoral approaches, those receiving treatment at non-academic or low case volume centers. These findings underscore the need for increased familiarity with these novel techniques, and the need to further delineate appropriate indications. Ongoing clinical trials will help to further define indications, functional outcomes, and oncologic outcomes associated with transoral surgery for OPSCC.
Background: Studies have demonstrated the feasibility as well as functional and oncologic outcomes for Transoral Robotic Surgery (TORS) for T1 and T2 oropharyngeal squamous cell carcinoma. The criticism of this emerging technology is its cost in a resource-constrained health care environment.

Methods: A societal perspective was adopted for the analysis. A decision analysis model was used to model costs and utilities of treatment and associated complications for TORS and definitive (chemo)radiotherapy. Remission and recurrence were modeled over a 10-year horizon using a Markov model. Relevant costs included hospital costs, professional fees, patient direct and lost productivity costs. Hospital costs were based on 57 patients undergoing TORS surgery and 30 patients undergoing definitive (chemo)radiotherapy for T1 and T2 oropharyngeal carcinomas. A systematic review of the literature was used to determine estimates of key model parameters (complications, recurrence, survival). Utility scores were determined for various health states using standard gamble methods. Quality adjusted life years (QALY) were determined for each treatment modality using the product of the life expectancy and the utility scores. Future costs and quality adjusted life years were discounted by 3%. Deterministic and probabilistic sensitivity analyses were used to test the robustness of the model. In probabilistic sensitivity analysis, costs of treatment, likelihood of recurrence, and utility weights were varied.

Results: In the base case analysis, patients treated with TORS received adjuvant therapy in 67% of cases, while patients treated with definitive radiotherapy received concurrent chemotherapy in 44% of cases. Relevant complications for TORS included: pharyngocutaneous fistula (2.5%), local hemorrhage (2.4%), hospital admission for dehydration/dysphagia (3%). Complications for radiotherapy (definitive and adjuvant) included: esophageal stenosis (4.8%), osteoradionecrosis (2.6%), and hospital admission for dehydration or febrile neutropenia (17%). One year tracheostomy and gastrostomy tube rates were (2.3% and 5%) for TORS and (0.8% and 7%) for (chemo)radiotherapy. Two year local, regional, and distant control rates were 95%, 95%, 97% for TORS and 96, 97, 87% for radiotherapy. In the base case analysis, over a 10 year time horizon, TORS dominated (chemo)radiotherapy resulting in a cost savings of $1,366 ($50,408 vs. $51,774) and an increase in quality adjusted life expectancy of 0.25 QALY (7.11 vs. 6.86 QALY) per treated case. In probabilistic sensitivity analysis, TORS was cost-effective (with 95% confidence) at a willingness to pay of $50,000 per increased QALY. Using a threshold sensitivity analysis, however, TORS ceased to be cost-effective as the proportion of adjuvant therapy reached 71% of cases. Using two-way sensitivity analysis, with a higher proportion of TORS patients receiving adjuvant therapy and a lower proportion of radiotherapy patients receiving concurrent chemotherapy, TORS is less cost-effective.

Conclusions: Transoral robotic surgery for the treatment of early T classification oropharyngeal carcinoma results in a cost savings and improved quality adjusted life expectancy. These findings are robust to fluctuations in key model parameters in probabilistic sensitivity analysis. However, with increasing likelihood of adjuvant therapy, TORS becomes less cost-effective. These findings suggest that case-selection is important to maintain the cost-effectiveness of this technology.
**FUNCTIONAL AND ONCOLOGICAL OUTCOMES IN TORS FOR OROPHARYNGEAL SCC**

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**Objective:** Transoral Robotic Surgery (TORS) has emerged as a first line therapy for early stage oropharyngeal squamous cell carcinoma (OPSCC). The primary objective of this study was to compare functional outcomes in OPSCC patients undergoing TORS alone, TORS and post-operative radiation (TORS+R), and TORS and post-operative chemoradiation (TORS+CR) using a dysphagia-specific quality-of-life measure, M.D. Anderson Dysphagia Inventory (MDADI), and a functional taste outcome measure, Scale of Subjective Total Taste Acuity (STTA). The secondary objective assessed the overall survival and disease free survival of OPSCC treated with TORS at a single institution.

**Study Design:** A retrospective review of prospectively collected data.

**Setting:** Single institution tertiary academic referral hospital of all patients undergoing TORS between 2007 and 2012 with at least 6 months follow-up were included.

**Methods:** Patients completed the MDADI and the STTA taste questionnaire (0: same taste acuity as before treatment, 1: mild loss of taste acuity, 2: moderate loss of taste acuity, 3: severe loss of taste acuity, 4: complete loss of taste acuity) at varying intervals following treatment. Clinical variables included age, stage, time of survey and HPV status. Multivariable linear regression was used to investigate the relationship between treatment modality and MDADI and taste assessment, adjusting for the age, stage, time of survey and HPV status. Regression coefficients ($\beta$) and standard errors (SE) were reported to compare linear regression models. The secondary objective was addressed by recording events including locoregional recurrence, metastatic disease and death.

**Results:** Fifty-seven patients completed the MDADI and STTA, 17 with TORS alone, 22 had TORS+R and 18 TORS+CR. The time to survey was similar across all three groups ($p=0.718$). The mean MDADI and STTA score for TORS was 95.2 and 0.35, TORS+R was 83.5 and 1.36, and TORS+CR was 76.7 and 1.5. The MDADI score was significantly affected by treatment modality (unadjusted $\beta_1=13.02$, SE=4.48, $p=0.005$) and the effect estimate remained significant when controlling for stage, age, time of survey and HPV status. Multivariable linear regression was used to investigate the relationship between treatment modality and MDADI and taste assessment, adjusting for the age, stage, time of survey and HPV status. Regression coefficients ($\beta$) and standard errors (SE) were reported to compare linear regression models. The secondary objective was addressed by recording events including locoregional recurrence, metastatic disease and death.

**Conclusion:** Patients with OPSCC suitable for treatment with TORS alone have excellent dysphagia specific quality of life and taste outcomes. The addition of postoperative radiation or chemoradiation to OPSCC patients treated with TORS significantly compromises dysphagia specific quality of life and taste function. In the TORS+R group, it appears that the higher the dose of postoperative radiation the greater the compromise of the MDADI and, therefore, limiting this dose may improve dysphagia specific quality of life.
TRANS-ORAL ROBOTIC SURGERY IMPROVES SURVIVAL COMPARED TO RADIATION AND/OR CHEMOTHERAPY FOR OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Objective: The rationale for the trans-oral robotic surgery (TORS) paradigm for oropharyngeal squamous cell carcinoma (OPC) is to reduce the toxic side effects associated with primary chemoradiation therapy. However, the survival outcome benefit of TORS as compared to primary radiation or chemoradiation has remained unclear. The aim of our study was to evaluate the effect of primary TORS on all-cause mortality (ACM) and disease-free survival (DFS) as compared to primary radiation or chemoradiation in patients with OPC.

Methods: We performed a retrospective study of OPC patients who received their initial primary treatment at the University of Pennsylvania Health System from 1/1/2010-12/31/2011, and sub-selected patients whose tumor p16 status was known. Patient demographic data, AJCC TNM stage, and treatment types were collected. Patient mortality and cancer recurrence status was current as of 10/1/2013. The outcomes were 2-year DFS and ACM. To adjust for potential confounding factors, we performed Cox regression analysis and calculated hazard ratios (HRs) to estimate the magnitude of the observed associations.

Results: Of the 313 OPC patients identified in the Penn Tumor Registry who underwent primary therapy, 214 had p16 testing. Of the 214 patients who underwent p16 testing, 122 patients received primary TORS with or without postoperative adjuvant therapy, and 55 patients received primary radiation or chemoradiation. The mean follow up time was 19 ± 8 months. The mean age at diagnosis was 59 ± 10 years; 90% were male (n=159); 89% were p16 positive (n=157); 3% were AJCC TNM stage 1 (n=5), 5% were stage 2 (n=9), 11% were stage 3 (n=19) and 81% were stage 4 (n=140). Among the primary TORS patients, 72% also received guideline-based postoperative radiation (n=88) and 43% received adjuvant chemoradiotherapy (n=52). All the primary radiation or chemoradiation patients received radiation and 91% had chemotherapy (n=50). The 2-year disease free survival rates were 82% in primary TORS patients (n=100) and 40% in primary radiation or chemoradiation patients (n=22). During 2-year follow-up, 6% of patients who had primary TORS died (n=7) and 15% patients had recurrence (n=18), while 15% patients with primary radiation or chemoradiation died (n=8) and 60% had recurrence (n=33). In addition, among the 157 p16 positive patients, primary TORS patients had 3% mortality rate (n=3) and 14% recurrence rate (n=16), while primary radiation and/or chemotherapy patients had 9% mortality rate (n=4) and 52% recurrence rate (n=23). After adjusting for demographic factors, p16 status, AJCC TNM stage and treatment types in the multiple Cox regression model, primary TORS significantly improved DFS (82% vs. 40%, adjusted-HR=0.19, 95%CI, 0.10-0.36, p<0.001) as compared to patients with radiation and/or chemotherapy as their primary treatment. There was no difference in all-cause mortality comparing the TORS and non-TORS patients (6% vs. 15%, adjusted-HR=0.28, 95%CI, 0.08-1.00, p=0.051).

Conclusion: In our single institution series, the use of TORS as a primary treatment regimen is associated with significantly improved disease free survival and cancer control in patients with oropharyngeal squamous cell cancer as compared to primary radiation or chemoradiation.
Objective: To compare outcomes of tonsil squamous cell carcinoma (SCCA) based on closest margin distance after resection of the primary tumor in patients who had single-modality treatment (transoral robotic surgery (TORS)) versus multi-modality treatment (TORS, radiotherapy and/or chemotherapy).

Study design: Retrospective cohort

Methods: Subjects that had undergone TORS at our institution between 2008 and 2013 for a tonsil primary and had negative margins at the time of surgery were included in the study. All patients had SCCA of the tonsil and all were alive at the end of the study period. Data on tumor size, closest margin distance, HPV status and postoperative radiation and/or chemotherapy was analyzed.

Results: 36 subjects were identified. 31 were male patients and 5 were female. Average age of the subjects was 58 years. 14 had a previous history of smoking. 30 patients were positive for HPV. The average size of the tumors was 2.29 cm with a range of 0.3 to 4.3 cm. The average distance to the closest margin was 1.6 mm with a margin range of 0.1 to 8 mm. 14 subjects had only TORS radical tonsillectomy and 22 patients TORS radical tonsillectomy with post-operative radiotherapy and/or chemotherapy. The average margin for patients who underwent TORS-only was 1.6 mm and those who underwent multimodality therapy was 1.7 mm. 10 of the patients who had TORS-only and 19 of the patients of the multimodality-therapy group were Stage III because of pathologic cervical adenopathy after neck dissection. Average follow-up for the cohort was 23 months. All the patients were alive at the end of the study period. At the present time there were no deaths in the cohort. There was one locoregional recurrence in a patient who had the largest tumor in the cohort. His tumor was smoking related and he was not adherent to radiotherapy.

Conclusion: In TORS radical tonsillectomy the closest margin from the tumor edge is 1 mm to 2 mm in the majority of cases. In this cohort of 36 patients tumor margin did not impact 2-year survival. Our preliminary data shows that in the presence of negative margins close margins do not change the outcome on patient survival at two years.
PROGNOSTIC SIGNIFICANCE OF MARGIN MAPPING IN TRANSORAL SURGERY FOR OROPHARYNGEAL SQUAMOUS CELL CARCINOMA
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Introduction:

The clinical and prognostic significance of margin size has become a point of debate with the increasing utilization of transoral surgery for oropharyngeal squamous cell carcinoma. The purpose of this study is to (1) evaluate the prognostic significance of margin status during transoral surgical treatment of primary oropharyngeal squamous cell carcinoma and (2) evaluate the prognostic significance of margin size at the peripheral and deep resection edges.

Methods:

After obtaining an IRB approval, a retrospective chart review was performed at a single tertiary academic medical center. Patients with previously untreated primary oropharyngeal squamous cell carcinomas undergoing transoral surgical resection between the years 1999 and 2012 were identified. All identified patients' pathology slides were reevaluated by a single reviewer with identification and quantification of margin size at both the peripheral and deep tumor edges. Results were then assessed for association with oncologic outcomes including local, regional, and distant disease recurrence as well as disease free survival, disease specific survival, and overall survival.

Results:

Two hundred and nineteen patients with oropharyngeal squamous cell carcinoma treated by primary surgical resection with or without adjuvant therapy were included in the study. Negative margins of resection were obtained in 204 patients (93.5%). Oncologic outcomes for the population as a whole revealed local recurrence in 3.7%, regional recurrence in 8.7%, and distant disease recurrence in 4.1% of patients. Comparing oncologic outcomes between patients with negative margins verses positive margins showed a statistically significant difference in local recurrence (4/15, 26.7% vs. 4/204, 2.0% respectively; p=0.0009), but no significant difference in regional recurrence (2/15, 13.3% vs. 17/204, 8.3% respectively; p=0.6256) or distant disease recurrence (1/15, 6.7% vs. 8/204, 3.9% respectively; p=0.4785). Kaplan-Meier 5-year estimation showed a statistically significant difference between patients with negative margins verses those with positive margins in disease free survival (60% vs. 88% respectively; p<0.001), disease specific survival (73% vs. 98% respectively; p<0.001), and overall survival (67% vs. 91% respectively; p<0.001). The maximum deep margin mean was 8.11 ± 0.52 mm and the minimum deep margin mean was 2.86 ± 0.27 mm. There was no significant relationship between the size of the maximum or minimum deep margin of resection with local, regional, or distant disease recurrence. The maximum peripheral mucosal margin mean was 8.56 ± 0.57 mm and the minimum peripheral mucosal margin mean was 3.41 ± 0.32 mm. There was no significant difference between the size of the maximum or minimum peripheral mucosal margin with local, regional, or distant disease recurrence.

Conclusions:

For primary oropharyngeal squamous cell carcinomas treated by transoral surgery, negative margins of primary tumor resection are associated with significantly improved oncologic outcomes. However, once
a negative margin is achieved, the size of the negative margin is not associated with oncologic outcomes for local, regional, or distant disease recurrence.
INCONSISTENCIES IN THE APPLICATION OF ADJUVANT THERAPY AFTER TRANSORAL ROBOTIC SURGERY (TORS) FOR HPV-ASSOCIATED OROPHARYNX SQUAMOUS CELL CARCINOMA

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Background:

Patients with human papillomavirus (HPV)-associated oropharynx squamous cell carcinoma (OPSCC) have a markedly improved prognosis compared to HPV negative patients. Numerous strategies to de-intensify treatment for HPV positive OPSCC patients are being investigated with the goal of reducing long-term toxicity. One method of de-intensifying treatment for patients with advanced-stage HPV-associated OPSCC includes the application of transoral robotic surgery (TORS) whereby select patients can be treated with a reduced dose of adjuvant radiation and/or spared chemotherapy. The purpose of this study was to explore potential variability in the application of adjuvant treatment after TORS for HPV-associated OPSCC.

Methods:

We conducted a retrospective review of TORS cases performed at Oregon Health and Science University (OHSU), a tertiary care medical center. The study was approved by the Institutional Review Board. Inclusion criteria were: 1) Stage III/IV OPSCC, 2) HPV positive by p16 immunohistochemistry, PCR testing or both, 3) treated with TORS, and 4) received adjuvant radiation therapy with or without chemotherapy. Demographic, clinicopathological and treatment characteristics were abstracted from the medical record. The dose of radiation therapy applied to the pharynx and the application of adjuvant chemotherapy were compared to current clinical trial protocols and consensus guidelines and analyzed descriptively.

Results:

A total of 127 TORS procedures were performed at OHSU between March 2010 and October 2013 for patients with OPSCC. 71 cases were excluded: early stage or recurrent cases not recommended adjuvant treatment (43); adjuvant treatment refused or not yet completed (9); HPV status negative or unknown (11); and patient lost to follow-up or deceased prior to treatment completion (8). Therefore, 56 patients were included in the final study with 47 men and 9 women, median age of 59 years (range 43-76). 40 patients (71%) received their radiation therapy away from OHSU.

Patients were stratified into low and high risk groups based on lymph node staging, surgical margins, and lymph node extracapsular spread. The low risk group (19) included patients with N1-N2 classification, negative margins and no extracapsular spread. Seven (37%) low risk patients received >6000 cGy to the pharynx, 10 (53%) received 6000 cGy and 2 (11%) received <6000 cGy. One (5.3%) low risk patient received adjuvant chemotherapy. The high risk group (37) included patients with >N2 classification, positive surgical margins and/or extracapsular spread. Of the high risk patients, 24 (65%) received >6000 cGy, 10 (27%) received 6000 cGy, and 3 (8%) received <6000 cGy. Consistent with current consensus guidelines, adjuvant chemotherapy was recommended to all patients with evidence of lymph node extracapsular spread (25). However, the choice of chemotherapy was not uniform: cisplatin (17), carboplatin/paclitaxel (3), and cetuximab (6).
With a median follow-up period of 13.8 months (range 4.5-40), 52 (93%) patients were alive without evidence of disease.

Conclusions:

There is significant heterogeneity in the application of adjuvant radiation and chemotherapy after TORS for HPV-associated OPSCC. The use of adjuvant treatments does not always correlate with clinicopathological factors and warrants further investigation.