Received: 15 November 2021 | Revised: 3 March 2022 | Accepted: 24 March 2022

DOI: 10.1002/hed.27045

ORIGINAL ARTICLE

WILEY

Transoral robotic surgery with neck dissection versus nonsurgical treatment in stage I and II human papillomavirus-negative oropharyngeal cancer

Craig A. Bollig MD[1] | **Brian Morris MD**[2] | **Vanessa C. Stubbs MD**[1]

[1]Department of Otolaryngology – Head and Neck Surgery, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

[2]Department of Surgery, Penn State College of Medicine, Hershey, Pennsylvania, USA

Correspondence
Craig A. Bollig, Department of Otolaryngology – Head and Neck Surgery, Rutgers Robert Wood Johnson Medical School, Brunswick, NJ 08901, USA.
Email: cbollig7@gmail.com

Section Editor: Neil Gross

Abstract

Background: Surgery + adjuvant therapy was shown to have improved overall survival (OS) versus nonsurgical treatment in T1-T2N1-N2b human papillomavirus (HPV)-negative oropharyngeal cancer (OPC). Our objective was to compare OS in transoral robotic surgery (TORS) with neck dissection versus nonsurgical treatment for T1-T2N0 HPV-negative OPC.

Methods: Patients with T1-T2N0 HPV-negative OPC were identified in the National Cancer Database. OS was compared between groups: (1) TORS with neck dissection +/− adjuvant therapy, (2) primary radiotherapy (>60 Gy) +/− chemotherapy using Kaplan–Meier and multivariable Cox proportional hazards models.

Results: There were 665 (78.4%) patients treated nonsurgically and 183 (21.6%) patients in the TORS group. Adjusting for age, comorbidity score, facility type, tumor subsite, and tumor stage, primary nonsurgical treatment was associated with worse OS (hazard ratio: 1.90, 95% CI: 1.34–2.69).

Conclusion: For T1-T2N0 HPV-negative OPC, TORS with neck dissection may be associated with a survival benefit over nonsurgical treatment.

KEYWORDS

human papillomavirus-negative, minimally invasive surgery, oropharyngeal cancer, radiation therapy, transoral robotic surgery

1 | INTRODUCTION

Oropharyngeal cancer (OPC) has become the most common subsite of head and neck cancers as a result of the increasing prevalence of human papillomavirus (HPV)-associated OPC.[1] The traditional surgical approaches to the oropharynx ranged from a simple tonsillectomy to a mandibulotomy or pharyngotomy, which may have also required complex reconstruction.[2] Overall, surgical resection with traditional techniques was shown to result in greater morbidity than nonsurgical treatment without improved oncologic outcomes.[3] With time, this lead to a predominance of radiation therapy-based treatment for

Accepted for presentation at the American Head and Neck Society Meeting, Dallas, April 2022.

OPC in the first part of this century.[3] More recently, the use of advanced, minimally invasive transoral surgical techniques to the oropharynx has been increasing, initially with transoral laser microsurgery (TLM) and later with transoral robotic surgery (TORS). TORS gained approval from the United States Food and Drug Administration in 2009 for early stage (T1 and T2) OPC. It has become adopted at many centers nationally, predominantly for HPV-positive OPC. In that population, TORS and radiation therapy based treatment have generally been shown to have similar oncologic outcomes; however, this question has not been as thoroughly investigated in HPV-negative OPC.[4–8] Biologically, HPV-negative tumors are more radioresistant than their HPV-positive counterparts, which has translated to worse oncologic outcomes in the former group.[9,10] In an attempt to better define the role for treatment intensification in this population, a randomized trial of transoral surgery (RTOG 1221) was initiated, but failed to accrue. In light of this, retrospective national databases like the National Cancer Database (NCDB) may provide the best available information on comparative outcomes at this time.[11] Recently, treatment intensification with surgery + adjuvant therapy was shown to have superior survival versus primary nonsurgical treatment in T1-T2, N1-N2b HPV-negative OPC in the NCDB and Surveillance, Epidemiology and End Results database (SEER).[12] However, there is a paucity of information on comparative outcomes of TORS versus nonsurgical treatment in early stage tumors without clinical evidence of nodal disease.[13] According to the current National Comprehensive Cancer Network (NCCN) guidelines, the subgroup of patients with stage I and II disease are candidates for single modality treatment.[14] The objective of this study was to compare overall survival (OS) between patients with stage I and II HPV-negative OPC undergoing TORS + neck dissection versus nonsurgical treatment using the NCDB. A secondary objective of this study was to identify clinical predictors of TORS in this population.

2 | MATERIALS AND METHODS

This project was exempt from full institutional review board review by Rutgers Robert Wood Johnson University Hospital in New Brunswick. We obtained the 2017 participant user file from the NCDB to perform a retrospective review of patients ≥18 years old diagnosed with squamous cell carcinoma of the oropharynx. The NCDB is a hospital based national registry maintained by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Cases are collected from >1500 facilities, encompassing approximately 70% of newly diagnosed cancers in the United States. There are established criteria to certify the quality of the submitted data, as well as an application process to obtain the data. After distribution of the data, the Commission on Cancer of the American College of Surgeons and the American Cancer Society are not responsible for the analysis and conclusions presented.

The NCDB was queried for all patients ≥18 years old with an OPC treated between 2010 and 2017 using topographic and morphologic codes from the International Classification of Disease for Oncology, 3rd Edition. Histologic codes included squamous cell carcinoma including variants (8070–8076, 8083). Topographical codes included the base of tongue/lingual tonsils [C01.9, C02.4], tonsil/lateral pharyngeal wall [C09.0, C09.1, C09.8, C09.9, C10.2], and other (soft palate [C05.1, C05.2], vallecula [C10.0], posterior pharyngeal wall [C10.3], and overlapping lesion/not otherwise specified [C10.8, C10.9]). HPV-negative OPC were identified by the NCDB variable indicating negative testing for HPV. Patients with clinically staged T1 and T2 tumors were included. Patients were excluded if they had distant metastatic disease (M1), carcinoma in situ disease, T3 or T4 tumors, clinically positive nodal disease, unknown HPV status, planned preoperative RT, neoadjuvant chemotherapy, or missing data. American Joint Committee on Cancer 7th edition was used for staging information.

The two treatment groups were then selected. The surgical group (TORS + neck dissection) included patients undergoing a robotic surgical resection along with a neck dissection (defined as examination of ≥5 lymph nodes), +/− adjuvant treatment. Patients were excluded if they had gross positive surgical margins (remaining tumor visible to the naked eye) or if no pathological specimen was sent, as these were considered debulking procedures or robotically assisted biopsies rather than an attempted definitive resection. The nonsurgical group included patients that received a total radiation dose of ≥60 Gy with or without chemotherapy, but no primary surgical procedure.

Baseline patient characteristics included a comparison of age, gender, race, insurance status, Charlson–Deyo comorbidity class (CDCC), location, facility type, tumor subsite, and tumor stage. Location was classified as metro (population > 250 000), urban (population 2500–250 000), and rural (population < 2500). Reported perioperative outcomes in the surgical group included median duration of hospital stay, surgical margin status, 30-day unplanned readmission rate, and 30-day mortality rate. Variables between treatment groups were then compared using the chi-square test or Fischer's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. Independent clinical predictors of

TABLE 1 Baseline patient characteristics

Characteristic	TORS + neck dissection, $n = 183$	(Chemo)radiotherapy, $n = 665$	p-value
Age			0.001
Median, (IQR)	60 (57–71)	61 (55–67)	
Sex			0.810
Male	125 (68.3%)	448 (67.4%)	
Female	58 (31.7%)	217 (32.6%)	
Race			0.208
White	167 (91.3%)	575 (86.5%)	
African American	14 (7.7%)	75 (11.3%)	
Other	2 (1.1%)	15 (2.3%)	
Insurance status			0.092
Private	77 (42.1%)	239 (35.9%)	
Medicaid	23 (12.6%)	58 (8.7%)	
Medicare	69 (37.7%)	311 (46.8%)	
Uninsured/other	14 (7.7%)	57 (8.6%)	
Location			0.220
Metro	147 (86.0%)	559 (85.5%)	
Urban	24 (14.0%)	84 (12.8%)	
Rural	0 (0.0%)	11 (1.7%)	
CDCC			0.772
0	135 (73.8%)	501 (75.3%)	
1	31 (16.9%)	113 (17.0%)	
≥2	17 (9.3%)	51 (7.7%)	
Facility type			<0.001
Academic	149 (83.2%)	257 (38.8%)	
Other	30 (16.8%)	405 (61.2%)	
Tumor subsite			<0.001
Tonsil	101 (55.2%)	248 (37.3%)	
Base of tongue	46 (25.1%)	187 (28.1%)	
Other	36 (19.7%)	230 (34.6%)	
Tumor stage			<0.001
T1	92 (50.3%)	163 (24.5%)	
T2	91 (49.7%)	502 (75.5%)	
Treatment received			
Surgery alone	135 (73.8%)		
Surgery + radiation therapy	31 (16.9%)		
Surgery + chemoradiotherapy	17 (9.3%)		
Primary radiation therapy		437 (65.7%)	
Primary chemoradiotherapy		228 (34.3%)	

Abbreviations: CDCC, Charlson–Deyo comorbidity class; IQR, interquartile range.

surgical treatment were analyzed using logistic regression. Variables that were statistically significant ($p < 0.10$) on univariable testing were then included in the initial multivariable logistic regression model. A backward elimination procedure was used to obtain a model containing only predictor variables whose coefficients were significant at the 0.05 level. Estimated odds ratios (OR) and associated 95% confidence intervals (CI)

were calculated for each model. Survival functions were estimated using the Kaplan–Meier (KM) method. OS was defined as the duration of time from the initial diagnosis until the date of death or last contact. OS was compared between surgical and nonsurgical treatment groups using the log-rank test as well as between treatment subgroups. A multivariable Cox proportional hazards model adjusting for age, comorbidity score, facility type, tumor subsite, and tumor stage was constructed for a less biased estimate of survival difference between treatment groups. These variables were selected a priori. Estimated hazards ratios (HR) and associated 95% CI were calculated for each model. Log minus log plots were used for testing the proportional hazards assumption. For all analyses, the threshold for statistical significance was set at $p < 0.05$. SPSS v26 software was used for data analysis (SPSS Inc., an IBM Company, Chicago, IL).

TABLE 2 TORS perioperative outcomes

Characteristic	
Hospital stay	
Median (IQR)	3 (2–7) days
Margins	
Negative	158 (86.3%)
Positive	25 (13.7%)
30 day unplanned readmissions	9 (4.9%)
30 day mortality	1 (0.5%)

Abbreviations: TORS, transoral robotic surgery; IQR, interquartile range.

3 | RESULTS

There were 848 patients remaining after exclusions. The majority were treated with nonsurgical treatment ($n = 665$, 78.4%). Of these, chemoradiotherapy was given in 228 (34.3%) patients, and radiotherapy alone was administered in 437 (65.7%) patients. There were 183 (21.3%) patients that were treated with TORS + neck dissection. Of these, the majority were treated with surgery alone ($n = 135$, 73.8%), and the remainder received adjuvant radiotherapy ($n = 31$, 16.9%) or chemoradiotherapy ($n = 17$, 9.3%). Table 1 describes the baseline patient characteristics for each treatment group. There were statistically significant differences in age, treating facility type, tumor subsite, and tumor stage between the two groups. Median follow-up was 34.2 months.

Table 2 describes the perioperative outcomes of TORS patients. The median hospital length of stay was 3 days (interquartile range 2–7). Positive margins occurred in 13.7% of cases ($n = 25$). The unplanned 30-day readmission rate was 4.9% ($n = 9$), and the 30-day mortality rate was 0.5% ($n = 1$).

The KM survival curves for the primary treatment groups are detailed in Figure 1. The 5-year OS for the entire cohort of T1-T2N0 patients was 55.8%, 95% CI: [51.5–60.1]. TORS was associated with improved OS versus nonsurgical treatment (5-year OS: 71.8%, 95% CI: [63.8–79.8] vs. 51.3%, 95% CI: [46.4–56.2], $p < 0.001$). Figure 2 displays the KM survival curves of the subgroups of each treatment category (TORS, TORS with adjuvant therapy, radiation therapy, chemoradiation therapy). There was no significant difference in OS between

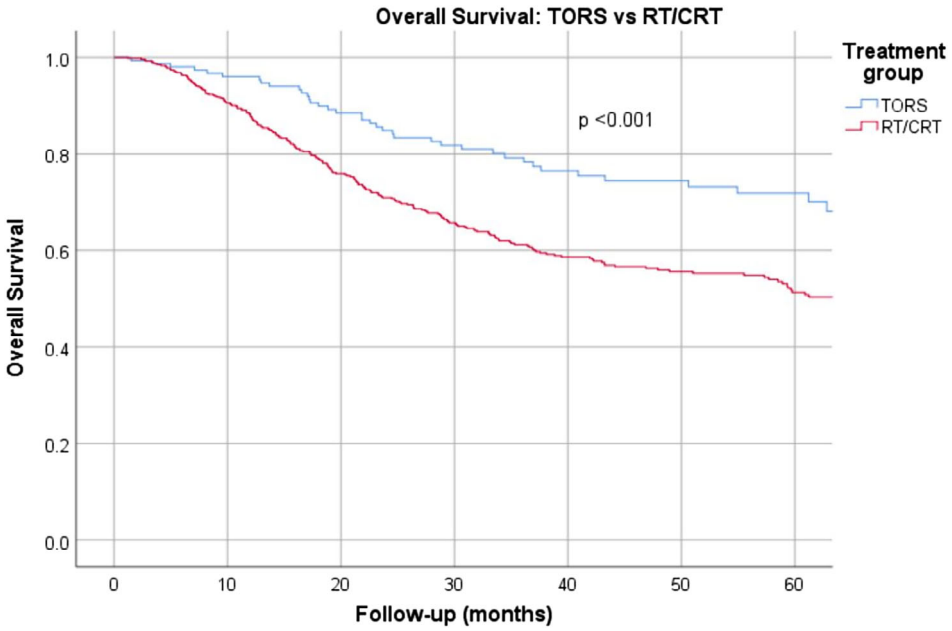

FIGURE 1 Kaplan–Meier plots demonstrating improved overall survival with TORS versus nonsurgical treatment [Color figure can be viewed at wileyonlinelibrary.com]

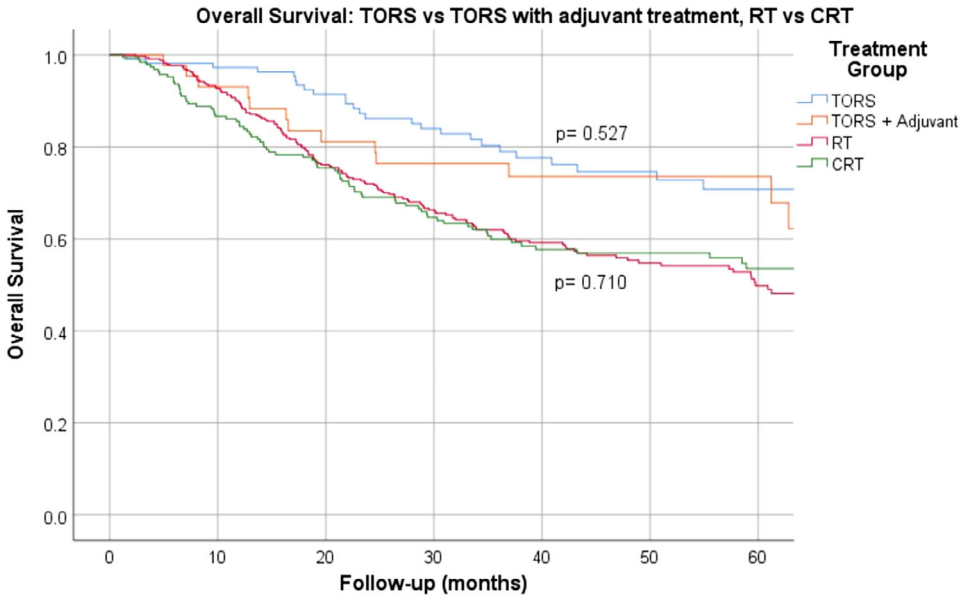

FIGURE 2 Kaplan–Meier plots for demonstrating no difference in overall survival between TORS with versus without adjuvant treatment ($p = 0.527$), or RT versus CRT ($p = 0.710$) [Color figure can be viewed at wileyonlinelibrary.com]

patients treated with primary radiation therapy versus chemoradiation therapy (5-year OS: 49.8%, 95% CI: [43.5–56.1], vs. 53.6%, 95% CI: [45.6–61.6], $p = 0.710$), or between patients treated with surgery alone versus surgery + adjuvant therapy (5-year OS: 70.8%, 95% CI: [60.6–81.0], vs. 73.5%, 95% CI: [60.0–87.0], $p = 0.527$).

Table 3 details the results of the multivariable Cox proportional hazards model adjusting for age, comorbidity score, facility type, tumor stage, and tumor subsite for a less biased comparison of treatment groups. In this model primary nonsurgical treatment was associated with worse OS versus TORS (HR: 1.90, 95% CI: 1.34–2.69). Additional factors significantly associated with OS were age (per 1 year) (HR: 1.03, 95% CI: 1.01–1.04) and CDCC ≥2 (HR: 2.30, 95% CI: 1.58–3.35). Treating facility type, tumor subsite, and tumor stage were not independently associated with survival.

Table 4 describes the multivariable analyses of the clinical factors associated with TORS. Age was no longer significantly associated with treatment type on these analyses. Treatment at an academic facility was the strongest predictor of TORS (OR: 7.72, 95% CI: 5.00–11.93). Tumors of the tonsil (OR: 2.70, 95% CI: 1.70–4.29) and T1 lesions (OR: 3.23, 95% CI: 2.20–4.72) were more likely to be treated with TORS versus other subsites and T2 tumors, respectively.

4 | DISCUSSION

Minimally invasive transoral surgical techniques, particularly TORS, have become increasingly utilized in the last decade.[5,15] National data indicates that the majority of T1 and T2 OPC are currently managed surgically; however, the majority of OPC cases are now HPV-associated.[5,15] Although oncologic outcomes appear to generally be equivalent between surgically based treatment and primary nonsurgical treatment in HPV-associated OPC, this may not be the case in HPV-negative OPC given the increased radioresistance in the latter.[9,10] Several recent institutional and national analyses of patients with HPV-negative OPC indicate generally favorable outcomes with surgically treated patients, including improved survival versus primary chemoradiation therapy patients with T1-T2N1-N2b disease.[12,16–19] This national review represents a complimentary analysis of the cohort of patients with T1-T2N0, HPV-negative OPC. The clinical factors predictive of TORS in this cohort were generally consistent with previous reports. Previously identified predictors of TORS versus nonsurgical treatment in OPC have included: younger age, race, female gender, higher comorbidity score, private insurance, tonsil primary site, smaller tumor stage, and decreasing nodal stage.[12,19,20]

Retrospective national data may provide the best available information on outcomes given the limitations in obtaining prospective randomized data in this population. In a noncomparative study using the NCDB, Jackson et al. reviewed 164 patients with T1-4 HPV-negative OPC undergoing TORS and found a 5-year OS of 78%, including a 5-year OS of 88% in the subgroup of patients with T1-T2N0-N1 disease.[18] There have been several national reviews utilizing the NCDB and/or SEER that have generally demonstrated improved survival outcomes in patients undergoing TORS versus nonsurgical

TABLE 3 Multivariable Cox proportional hazards model for overall survival

Characteristic	Hazard ratio	95% confidence interval	*p*-value
Treatment strategy			
TORS +/− (C)RT	Ref.		
Primary (C)RT	1.90	[1.34–2.69]	<0.001
Age (per 1 year)	1.03	[1.01–1.04]	<0.001
CDCC			
0	Ref.		
1	1.17	[0.85–1.61]	0.319
≥2	2.30	[1.58–3.35]	<0.001
Facility type			
Academic	0.96	[0.75–1.23]	0.667
Other	Ref.		
Tumor subsite			
Base of tongue	1.16	[0.87–1.55]	0.304
Tonsil	Ref.		
Other	1.16	[0.86–1.55]	0.351
Tumor stage			
T1	Ref.		
T2	1.06	[0.81–1.39]	0.809

Abbreviations: CDCC, Charlson–Deyo comorbidity class; (C)RT, (chemo)radiotherapy; IQR, interquartile range; TORS, transoral robotic surgery.

TABLE 4 Clinical variables associated with TORS on multivariable analyses

Clinical factor	Odds ratio	95% confidence interval	*p*-value
Tumor stage			
T1	3.23	[2.20–4.72]	<0.001
T2	Ref.		
Primary site			
Tonsil	2.70	[1.70–4.29]	<0.001
Base of tongue	1.65	[0.98–2.80]	0.060
Other	Ref.		
Facility type			
Academic	7.72	[5.00–11.93]	<0.001
Nonacademic	Ref.		

Abbreviation: TORS, transoral robotic surgery.

treatment.[12,19] In 2018 Mahmoud et al. reviewed 515 patients in the NCDB with T1-T4 HPV-negative disease and found a survival advantage in HPV-negative patients treated with TORS versus those who received at least 50 Gray of primary radiation therapy +/− chemotherapy (3 year OS: 84% vs. 66%, respectively).[19] Likewise, in a thorough analysis of the NCDB and SEER, Jacobs et al. analyzed 3004 patients in the NCDB and 670 in the SEER database with T1-T2, N1-N2b HPV-negative OPC undergoing surgery (all approaches) with adjuvant therapy versus nonsurgical treatment and found improved OS and disease-specific survival in the surgical cohort.[12] On the other hand, several earlier evaluations of the NCDB did not find a significant difference in outcomes between treatment groups, although their populations differed from this analysis.[21,22] The analysis by Baliga et al. included patients with HPV+ disease and unknown HPV status, and did not require surgical treatment to include nodal evaluation.[21] The study by Kelly et al. included patients with T1-T2N1-N2b HPV-negative OPC undergoing surgical resection (all approaches) with or without a neck dissection from 2010 to 2012.[22] It is noteworthy that

the same institution later performed a more thorough analysis of that population utilizing the NCDB and SEER over a broader timeframe (2010–2016) and found improved OS and disease-specific survival in the surgical cohort.[12] Aside from the inclusion of different years, reasons for the survival differences between studies that Jacobs et al. propose include (1) their study required nodal evaluation in addition to surgical resection, which is considered the standard of care; (2) the substantial amount of missing data for HPV status in the early years of the NCDB and SEER.[12] The latter reporting bias may have been associated with systematic differences between institutions that reported HPV status in the earlier years versus those that did not.[12] Similar to the more recent reports, we found a survival advantage associated with upfront surgical treatment in both the unadjusted survival analyses and multivariable Cox proportional hazards models accounting for known confounding variables.

Results from institutional series are limited by small sample size given the changing epidemiologic trends of OPC, but mirror national data.[16,17,23] In the largest single institution review of 56 patients with T1-T4N0-N2c HPV-negative OPC, Parhar et al. reported a 3-year OS and locoregional control rate of 85.5% and 84.4%, respectively.[23] Negative surgical margins were obtained in 80.4% of patients. Crude swallowing outcomes were favorable as well.[23] Only 5.4% of patients required a gastrostomy tube at 1 year, 23.2% received a gastrostomy tube perioperatively or during adjuvant therapy.[23] These results come in contrast to earlier work in the pre-TORS era demonstrating comparable oncologic outcomes between surgically based treatment versus radiation therapy based treatment, with more severe or fatal complications occurring in surgically treated patients.[3,24] As a consequence, this established radiation therapy as the dominant treatment modality at most centers.[3,24] However, minimally invasive techniques are associated with significantly less morbidity than the traditional approaches and may optimize oncologic outcomes, as well.[25,26] In multiple national studies, TORS has been associated with reduced margin positivity and improved OS in patients with OPC versus other surgical approaches.[15,27] The positive margin rate in this cohort was very favorable at 13.7%. Nguyen et al. postulated the survival benefit may be due to the technical advantages of TORS including improved visualization angles, magnified views, increased range of motion, and ability to use en bloc resection techniques.[15] Alternatively, they propose it may be a surrogate for surgical experience, volume, or acumen since they found increased lymph node yield during neck dissection in patients undergoing TORS.[15]

In appropriate candidates, TORS may offer several advantages over radiotherapy including increased cost-effectiveness, repeatability in select recurrent cases or second primary malignancies, risk stratification with pathologic information, and treatment intensification in high-risk patients. Several cost-effectiveness analyses have demonstrated increased cost-effectiveness of TORS versus radiation therapy for early T-stage OPC, although this is predicated on the rate of adjuvant therapy and quality of life assumptions.[28–31] Appropriate case selection optimizes cost effectiveness by reducing the rates of adjuvant therapy administration. In this national cohort of patients without clinically positive lymph nodes, adjuvant therapy rates were very favorable (26.2%). Increasing use of concurrent chemotherapy also has a significant impact on the cost-effectiveness of each treatment arm.[31] Interestingly, despite radiation therapy alone as a recommended treatment modality by the NCCN guidelines for T1-T2N0 disease, approximately 1/3 of patients in the nonsurgical cohort received chemoradiation therapy. This was not associated with improved OS in this cohort. TORS has been shown to be safely and effectively utilized in the recurrent setting as well as in second primary oropharyngeal malignancies.[25,32] Additionally, as a single modality, surgery provides the advantage of a one-time treatment versus repeated daily treatments over several weeks. The acute toxicity of radiation therapy is well described in the literature, which can lead to interruptions or early discontinuation of treatment.[33,34] In a SEER database review, Fesinmeyer et al. reported that nearly 40% of patients undergoing head and neck radiation therapy had an interruption or early discontinuation of treatment, potentially negatively impacting oncologic outcomes.[33] This occurred more commonly in nonsurgical patients versus those undergoing adjuvant treatment (52% vs. 70%, respectively).[33] Also in their analysis, the use of concurrent chemotherapy was associated with a decreased likelihood of completing treatment.[33] Finally, surgical resection provides a pathologic specimen to identify high-risk pathologic features, and the ability to tailor the use of risk-directed adjuvant therapy in appropriate patients.

Functional outcomes after TORS are well-documented in the literature, primarily in HPV-associated OPC.[35–38] They can likely be transferrable to similarly staged HPV-negative OPC. However, there remains significant controversy on how functional outcomes compare between TORS versus radiation therapy. This is particularly true in patients undergoing TORS that also receive adjuvant therapy, which is adversely associated with swallowing outcomes compared to surgery alone.[35–38] The phase 2 ORATOR trial, which randomized 68 patients with T1-T2N0-N2b to TORS versus nonsurgical treatment found

no clinically significant difference in swallowing outcomes at 1 year between the two groups.[7] However, a large portion of the surgical group also received adjuvant therapy (71%).[7] Functional outcomes after TORS alone compare very favorably with nonsurgical treatment, with some reporting superior results with TORS.[35] In a retrospective cohort study of 76 patients with T1-T2, N0-N1 HPV-associated OPC, Xu compared five different quality of life (QOL) questionnaires in patients undergoing TORS alone, TORS with adjuvant treatment, and nonsurgical treatment.[35] Surgical treatment alone resulted in the best associated QOL, while surgery with adjuvant therapy and primary nonsurgical treatment were associated with similar QOL scores.[35]

This study included a number of limitations. Selection bias is inherent in retrospective studies, but multivariable models were utilized to assess the impact of known confounding variables. The NCDB does not contain information regarding certain high-risk features (e.g., perineural invasion), disease recurrence, previous treatment, or cause of death. Therefore, our oncologic outcome analysis was restricted to overall survival. The lack of this information potentially obscures the beneficial effect of adjuvant therapy in this population. Although the NCDB offers several benefits over other databases, coding errors and incomplete/missing data are inherent to database studies. Finally, data on functional outcomes are not available in the NCDB, but compose an integral role in treatment decision-making in head and neck cancer in addition to oncologic outcomes.

In conclusion, there is growing evidence that in appropriate candidates, TORS offers favorable oncologic outcomes in HPV-negative OPC. Recent work by Jacobs et al. demonstrated that surgical treatment was associated with improved OS in patients with T1-T2N1-N2b disease in the NCDB and SEER.[12] We performed a complimentary NCDB analysis of the subgroup of patients with T1-T2N0 disease, and found similar results. Given the challenges in obtaining data from randomized trials in this population, national databases, while subject to limitations, currently offer the best available evidence. Treatment decisions should be made in the context of a multidisciplinary tumor board discussion, evaluation of patient specific clinical factors that may influence treatment, and patient preference. This analysis found potential disparities with access to TORS at nonacademic centers. With growing evidence of the potential survival advantage with primary surgical treatment, evaluation of all patients by a head and neck surgical oncologist with training in TORS or TLM for consideration of surgical treatment, along with a radiation oncologist would optimize oncologic care and enhance access to both treatment modalities.

5 | CONCLUSIONS

TORS may offer a survival advantage in patients with T1-T2N0 HPV-negative OPC compared to primary nonsurgical treatment. Given the lack of available prospective data, TORS should be strongly considered for appropriate candidates.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

ORCID

Craig A. Bollig https://orcid.org/0000-0002-9514-5338

REFERENCES

1. Ellington TD, Henley SJ, Senkomago V, et al. Trends in incidence of cancers of the oral cavity and pharynx – United States 2007–2016. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):433-438.
2. Holsinger FC, Laccourreye O, Weber RS. Surgical approaches to the oropharynx. *Oper Tech Otolaryngol Head Neck Surg*. 2005;16:40-48.
3. Parsons JT, Mendenhall WM, Stringer SP, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. *Cancer*. 2002;94(11):2967-2980.
4. Parhar HS, Yver CM, Brody RM. Current indications for transoral robotic surgery in oropharyngeal cancer. *Otolaryngol Clin North Am*. 2020;53(6):949-964.
5. Cracchiolo JR, Baxi SS, Morris LG, et al. Increase in primary surgical treatment of T1 and T2 oropharyngeal squamous cell carcinoma and rates of adverse pathologic features: National Cancer Data Base. *Cancer*. 2016;122(10):1523-1532.
6. Howard J, Masterson L, Dwivedi RC, et al. Minimally invasive surgery versus radiotherapy/chemoradiotherapy for small-volume primary oropharyngeal carcinoma. *Cochrane Database Syst Rev*. 2016;12(12):CD010963.
7. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. *Lancet Oncol*. 2019;20(10):1349-1359.
8. Monnier Y, Simon C. Surgery versus radiotherapy for early oropharyngeal tumors: a never-ending debate. *Curr Treat Options Oncol*. 2015;16(9):42.
9. Kimple RJ, Smith MA, Blitzer GC, et al. Enhanced radiation sensitivity in HPV-positive head and neck cancer. *Cancer Res*. 2013;73(15):4791-4800.
10. Blitzer GC, Smith MA, Harris SL, Kimple RJ. Review of the clinical and biologic aspects of human papillomavirus–positive squamous cell carcinomas of the head and neck. *Int J Radiat Oncol Biol Phys*. 2014;88(4):761-770.
11. RTOG. Radiation therapy and cisplatin with or without surgery in treating patients with stage III-IV oropharyngeal cancer.

https://clinical trials.gov/ct2/show/record/NCT01953952. Published 2013. Accessed August 22, 2021.
12. Jacobs D, Torabi SJ, Park HS, et al. Revisiting the radiation therapy oncology group 1221 hypothesis: treatment for stage III/IV HPV-negative oropharyngeal cancer. *Otolaryngol Head Neck Surg*. 2021;164(6):1240-1248.
13. Sload R, Silver N, Jawad BA, Gross ND. The role of transoral robotic surgery in the management of HPV negative oropharyngeal squamous cell carcinoma. *Curr Oncol Rep*. 2016;18(9):53.
14. Head and Neck Cancer. Version 3.2021. *NCCN Clinical Practice Guidelines in Oncology*. National Comprehensive Cancer Network; 2021.
15. Nguyen AT, Luu M, Mallen-St Clair J, et al. Comparison of survival after transoral robotic surgery vs nonrobotic surgery in patients with early-stage oropharyngeal squamous cell carcinoma. *JAMA Oncol*. 2020;6(10):1555-1562.
16. Stucken CL, de Almeida JR, Sikora AG, Tong CC, Genden EM. Impact of human papillomavirus and smoking on survival outcomes after transoral robotic surgery. *Head Neck*. 2016;38(3):380-386.
17. de Almeida JR, Li R, Magnuson JS, et al. Oncologic outcomes after transoral robotic surgery: a multi-institutional study. *JAMA Otolaryngol Head Neck Surg*. 2015;141(12):1043-1051.
18. Jackson RS, Stepan K, Bollig C, et al. Outcomes of HPV-negative oropharyngeal cancer treated with transoral robotic surgery. *Otolaryngol Head Neck Surg*. 2021;165:682-689.
19. Mahmoud O, Sung K, Civantos FJ, Thomas GR, Samuels MA. Transoral robotic surgery for oropharyngeal squamous cell carcinoma in the era of human papillomavirus. *Head Neck*. 2018;40(4):710-721.
20. Berger MH, Yasaka TM, Haidar YM, Kuan EC, Tjoa T. Insurance status as a predictor of treatment in human papillomavirus positive oropharyngeal cancer. *Laryngoscope*. 2021;131(4):776-781.
21. Baliga S, Kabarriti R, Jiang J, et al. Utilization of transoral robotic surgery (TORS) in patients with oropharyngeal squamous cell carcinoma and its impact on survival and use of chemotherapy. *Oral Oncol*. 2018;86:75-80.
22. Kelly JR, Park HS, An Y, et al. Comparison of survival outcomes among human papillomavirus–negative cT1-2 N1-2b patients with oropharyngeal squamous cell cancer treated with upfront surgery vs definitive chemoradiation therapy: an observational study. *JAMA Oncol*. 2017;3(8):1107-1111.
23. Parhar HS, Weinstein GS, O'Malley BW Jr, et al. Oncologic outcomes of transoral robotic surgery for HPV-negative oropharyngeal carcinomas. *Head Neck*. 2021;43:2923-2934.
24. Chen AY, Zhu J, Fedewa S. Temporal trends in oropharyngeal cancer treatment and survival: 1998–2009. *Laryngoscope*. 2014;124(1):131-138.
25. White H, Ford S, Bush B, et al. Salvage surgery for recurrent cancers of the oropharynx: comparing TORS with standard open surgical approaches. *JAMA Otolaryngol Head Neck Surg*. 2013;139(8):773-778.
26. Lee SY, Park YM, Byeon HK, Choi EC, Kim SH. Comparison of oncologic and functional outcomes after transoral robotic lateral oropharyngectomy versus conventional surgery for T1 to T3 tonsillar cancer. *Head Neck*. 2014;36(8):1138-1145.
27. Chillakuru Y, Benito DA, Strum D, et al. Transoral robotic surgery versus nonrobotic resection of oropharyngeal squamous cell carcinoma. *Head Neck*. 2021;43(7):2259-2273.
28. Thankappan K, Battoo AJ, Vidhyadharan S, Kudpaje A, Balasubramanian D, Iyer S. Economic evaluations comparing tran-oral robotic surgery and radiotherapy in oropharyngeal squamous cell carcinoma: a systematic review. *Eur J Surg Oncol*. 2021;47(12):2961-2970.
29. Spellman J, Coulter M, Kawatkar A, Calzada G. Comparative cost of transoral robotic surgery and radiotherapy (IMRT) in early stage tonsil cancer. *Am J Otolaryngol*. 2020;41(3):102409.
30. Rodin D, Caulley L, Burger E, et al. Cost-effectiveness analysis of radiation therapy versus transoral robotic surgery for oropharyngeal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2017;97(4):709-717.
31. de Almeida JR, Moskowitz AJ, Miles BA, et al. Cost-effectiveness of transoral robotic surgery versus (chemo)radiotherapy for early T classification oropharyngeal carcinoma: a cost-utility analysis. *Head Neck*. 2016;38(4):589-600.
32. Bollig CA, Lee DS, Mazul AL, et al. Systematic review of second primary oropharyngeal cancers in patients with p16+ oropharyngeal cancer. *Otolaryngol Head Neck Surg*. 2021;164(4):733-740.
33. Fesinmeyer MD, Mehta V, Tock L, Blough D, McDermott C, Ramsey SD. Completion of radiotherapy for local and regional head and neck cancer in Medicare. *Arch Otolaryngol Head Neck Surg*. 2009;135(9):860-867.
34. Thomas K, Martin T, Gao A, Ahn C, Wilhelm H, Schwartz DL. Interruptions of head and neck radiotherapy across insured and indigent patient populations. *J Oncol Pract*. 2017;13(4):e319-e328.
35. Xu MJ, Plonowska KA, Gurman ZR, et al. Treatment modality impact on quality of life for human papillomavirus-associated oropharynx cancer. *Laryngoscope*. 2020;130(2):E48-E56.
36. Sethia R, Yumusakhuylu AC, Ozbay I, et al. Quality of life outcomes of transoral robotic surgery with or without adjuvant therapy for oropharyngeal cancer. *Laryngoscope*. 2018;128(2):403-411.
37. Dziegielewski PT, Teknos TN, Durmus K, et al. Transoral robotic surgery for oropharyngeal cancer: long-term quality of life and functional outcomes. *JAMA Otolaryngol Head Neck Surg*. 2013;139(11):1099-1108.
38. Hutcheson KA, Warneke CL, Yao CMKL, et al. Dysphagia after primary transoral robotic surgery with neck dissection vs nonsurgical therapy in patients with low- to intermediate-risk oropharyngeal cancer. *JAMA Otolaryngol Head Neck Surg*. 2019;145(11):1053-1063.

How to cite this article: Bollig CA, Morris B, Stubbs VC. Transoral robotic surgery with neck dissection versus nonsurgical treatment in stage I and II human papillomavirus-negative oropharyngeal cancer. *Head & Neck*. 2022;44(7):1545-1553. doi:10.1002/hed.27045