Original Article

Triple-Modality Treatment in Patients With Advanced Stage Tonsil Cancer

Dylan F. Roden, MD, MPH [1,2]; David Schreiber, MD[2,3]; and Babak Givi, MD[1,2]

BACKGROUND: Concurrent chemoradiation (CCRT) and upfront surgery followed by adjuvant therapy both are recommended treatment options for patients with advanced stage squamous cell carcinoma (SCC) of the tonsil. To the authors' knowledge, the question of whether surgical-based treatments can achieve better survival compared with CCRT has never been compared in a clinical trial. The authors analyzed the National Cancer Data Base to measure the impact of different treatment modalities on overall survival (OS). **METHODS:** All patients aged ≤70 years diagnosed with clinical stage III to IVB (excluding T4B) SCC of the tonsil from 1998 through 2011 were selected. Analysis was limited to patients receiving CCRT, surgery plus CCRT, or surgery followed by adjuvant radiotherapy (RT). OS was compared using the Kaplan-Meier method and log-rank test. Univariable and multivariable hazards analyses were performed to identify factors significant for survival. Propensity score matching was performed. **RESULTS:** There were 16,891 patients who met the inclusion criteria. The most common treatment was CCRT (8123 patients; 48.1%), followed by surgery plus CCRT (5249; 31.1%) and surgery plus RT (3519 patients; 20.8%). Patients treated with surgery plus CCRT were found to have the highest 3-year OS rate (88.5%) followed by those treated with surgery plus RT (84%) and CCRT (74.2%) ($P<.0001$). In a propensity score-matched subpopulation of 4962 patients, the 3-year OS rate was 90.2% for those treated with surgery plus CCRT, 84.9% for those treated with surgery plus RT, and 82.1% for those treated with definitive CCRT ($P<.0001$). **CONCLUSIONS:** Patients with advanced stage SCC of the tonsil who underwent surgery followed by CCRT had the greatest OS. Patients undergoing upfront surgery may avoid chemotherapy without jeopardizing survival. Triple-modality therapy may provide a survival benefit for a subset of patients with advanced stage tonsil cancer. ***Cancer* 2017;123:3269-76**. © *2017 American Cancer Society.*

KEYWORDS: cancer, multimodality, National Cancer Data Base, squamous cell carcinoma (SCC), survival, tonsil.

INTRODUCTION

The current National Comprehensive Cancer Network guidelines for patients with advanced stage oropharyngeal cancer recommend 3 different treatment options: definitive concurrent chemoradiation (CCRT), surgery followed by appropriately selected adjuvant therapy (radiotherapy [RT] alone or CCRT depending on pathologic features), or induction chemotherapy followed by RT or CCRT.[1] Although these treatments are believed to have equivalent survival outcomes, to the best of our knowledge this hypothesis has never been tested in the setting of a randomized clinical trial.

Although all patients with cancer of the oropharynx are treated similarly, the oropharynx consists of 3 distinct subsites: the base of the tongue, palatine tonsils, and the posterior pharyngeal wall. The principles of organ preservation might not be as applicable to the tonsil subsite, because the tonsil does not have any critical function in the adult. The morbidity of a radical tonsillectomy is less than that of a base-of-tongue resection. Excluding open approaches, a base-of-tongue resection requires transoral robotic surgery (TORS) or advanced transoral laser microsurgery techniques, whereas a radical tonsillectomy can be adequately performed with commonly available surgical instrumentation and traditional techniques.

Recognizing these differences between the base of the tongue and the tonsil, we compared survival outcomes among patients with advanced stage cancer of the tonsil who were treated with definitive CCRT versus upfront surgery using the National Cancer Data Base (NCDB), which is one of the largest publically available cancer databases in the United States. Our secondary aim was to determine whether triple-modality treatment (surgery followed by adjuvant CCRT) afforded any survival benefit for patients with advanced stage tonsil cancer.

MATERIALS AND METHODS

The NCDB is a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is estimated that approximately 70% of all diagnosed malignancies in the United States are captured by facilities participating in this registry and reported to the NCDB. The Commission on Cancer's NCDB and the hospitals

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participating in the NCDB are the source of the deidentified data used in the current study. However, the NCDB has not verified and is not responsible for the statistical validity or conclusions derived herein. The current study was deemed exempt by our Institutional Review Board.

We selected all patients in the NCDB diagnosed from 1998 through 2011 with squamous cell carcinoma (SCC) of the tonsil. Tonsil subsite was defined by *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) codes C09.0, C09.1, and CO9.9. SCC included ICD-O-3 histology codes 8070 through 8078, and 8083 (basaloid SCC).

We excluded all patients who had overall clinical stage I or II disease. All patients presenting with T4B disease also were excluded. All patients presenting with metastatic disease were excluded. All stages were based on the pretreatment clinical stage as documented in the NCDB. The remaining patients formed the study cohort.

The objective of the current study was to compare the 3 most common treatment modalities, namely CCRT, surgery followed by adjuvant RT, and surgery followed by adjuvant CCRT. Patients for whom there was incomplete treatment information or patients treated with any modalities other than these 3 options were excluded from the current analysis. Patients also were excluded if they were treated with palliative intent. Patients treated with surgery were included if they underwent partial pharyngectomy, local tumor excision not otherwise specified (NOS), or other procedures. Patients who underwent simple and excisional biopsies were excluded from the surgical cohorts. Surgical treatment of the neck was recorded as completed or not for purposes of analysis. To ensure that chemotherapy and RT were delivered concurrently, we used an absolute value of 14 days from the initiation of either therapy as a cutoff for exclusion. Patients who were aged >70 years were excluded from the analysis.

Statistical Analysis

Overall survival (OS) was calculated using the Kaplan-Meier method. Differences in survival were compared between different treatments using the log-rank test. We conducted uninvariable hazards analysis to identify factors significant for survival. Age, year of diagnosis, Charlson-Deyo comorbidity score (comorbidity score of 0, 1, 2, or unknown), race (white, black, or other), insurance status (private, public, uninsured, or unknown), tumor classification (T1, T2, T3, or T4), lymph node classification (N0, N1, N2A, N2B, N2C, N2NOS, and N3), and treatment (CCRT, surgery plus RT, or surgery plus CCRT) were selected. A Cox proportional hazards model was built including these 8 variables.

A secondary analysis was performed on a propensity score-matched subpopulation, matching for age, T classification, N classification, race, comorbidity, insurance status, and year of diagnosis. Propensity score matching was performed with a binary treatment indicator of upfront CCRT versus upfront surgery, which included both surgery plus RT and surgery plus CCRT. A nearest neighbor matching algorithm was used with a caliper of 0.0005. An additional analysis was performed on a propensity score-matched subpopulation, in the same manner as previously described, except this analysis compared the 2 dual-modality treatment groups: CCRT versus surgery plus RT.

All analysis was performed using SPSS statistical software (version 23; IBM Corporation, Armonk, NY). A P value $<.05$ was used to determine statistical significance.

RESULTS

We identified 57,544 patients with SCC of the tonsil diagnosed from 1998 through 2011. Figure 1 demonstrates how the exclusion criteria were applied. Ultimately, 16,891 patients met all the inclusion criteria and formed the study population.

Table 1 captures demographic information. The median age of the patients was 55 years, 83.5% were male, and 90.9% were white. A majority of patients had private insurance (63.1%). The most common treatment modality was CCRT (48.1%), followed by surgery plus CCRT (31.1%), and surgery plus RT (20.8%). There were 8768 patients who underwent surgery as part of their treatment; 69.8% underwent partial pharyngectomy, 10.2% underwent local tumor excision NOS, and 20% underwent another form of surgery. In analyzing patients who underwent surgery as part of their treatment, 74.2% underwent concomitant surgical neck dissection. A significant minority of patients treated with surgery (40%) avoided chemotherapy. The median dose of RT delivered in the CCRT group was 70 Grays (Gy) (interquartile range, 56-72 Gy), whereas the median dose of RT delivered in both the surgery plus RT and surgery plus CCRT groups was 66 Gy (interquartile range, 54-70 Gy). Positive surgical margins were reported in 31% of the surgical group (Table 2).

There were 4549 deaths (26.9%) reported during the study period, with a median follow-up of 44.8 months. Patients who underwent surgery followed by CCRT were found to have the greatest 3-year OS rate (88.5%), followed by those who underwent surgery plus

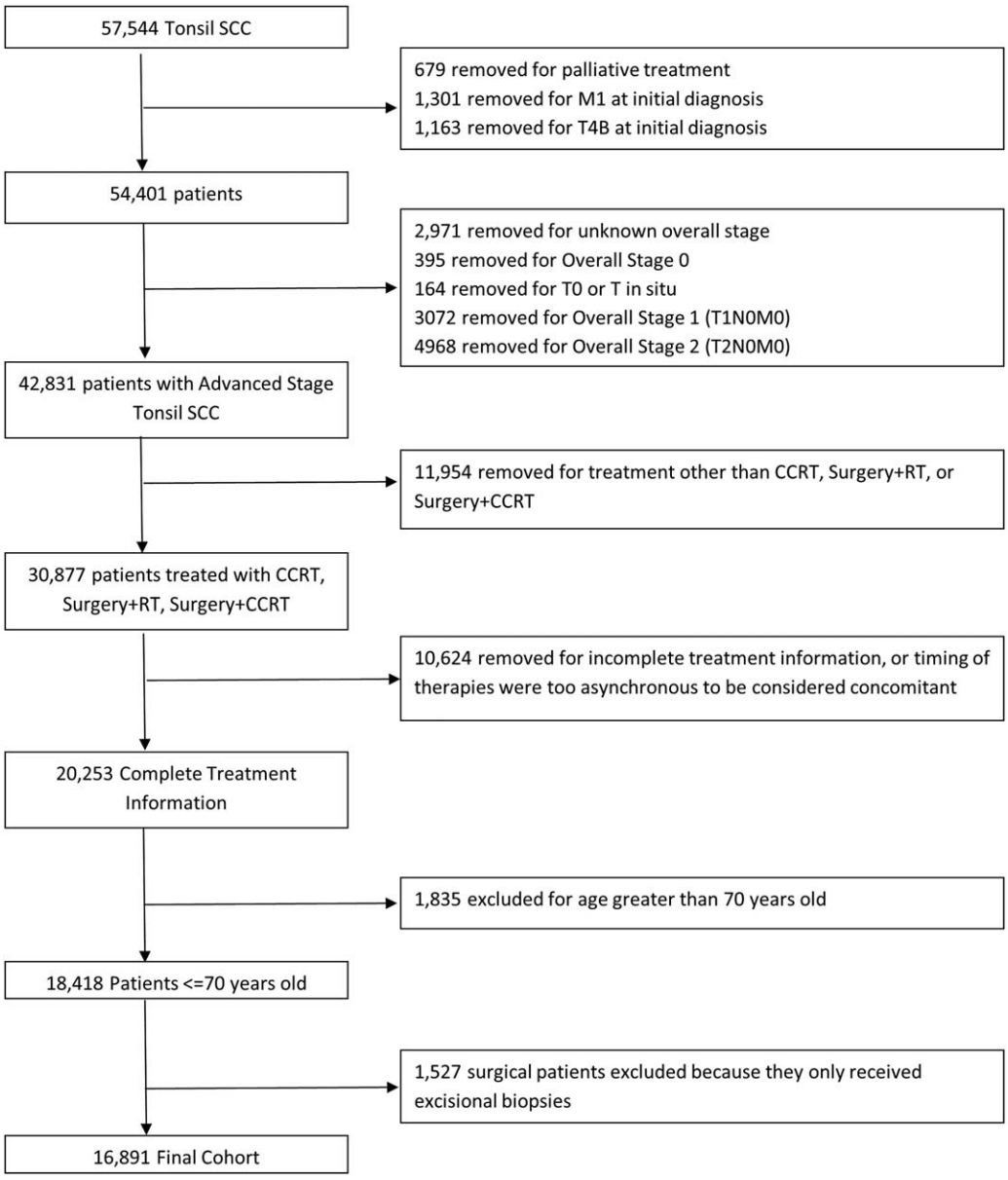

Figure 1. Study exclusion criteria and flow chart. CCRT indicates concurrent chemoradiation; RT, radiotherapy; SCC, squamous cell carcinoma. All staging are based on pretreatment clinical stage.

RT (84%) and those who underwent CCRT (74.2%) ($P<.001$) (Fig. 2). The median survival for patients who underwent surgery plus CCRT was not reached, the median survival for those treated with surgery plus RT was 168.3 months, and the median survival for those who underwent CCRT was 112.1 months ($P<.001$).

Table 3 shows the univariable and multivariable hazards analysis for OS. The most significant factors found to be associated with death on univariable hazards analysis were a tumor classification of T4, black race, advanced Charlson/Deyo comorbidity score, and insurance status. Surgical treatments were associated with improved survival. All these factors retained their statistical significance on the multivariable hazards model. Both treatment with surgery plus RT and surgery plus CCRT were found to be associated with improved survival in the multivariable model (hazard ratio [HR] of 0.82 and HR of 0.68, respectively; $P<.001$).

Propensity score matching produced a matched cohort of 4962 patients. The overall balance test statistic chi-square was 8.213 with 7 degrees of freedom ($P = .31$), indicating successful balance based on the input covariates.

TABLE 1. Demographic Characteristics[a]

Characteristic	N = 16,891
Median age, y	55
Male sex	14,102 (83.5%)
Race	
White	15,347 (90.9%)
Black	1350 (8%)
Other	194 (1.1%)
Insurance status	
Private	10,650 (63.1%)
Government	4469 (26.5%)
Uninsured	1045 (6.2%)
Unknown	727 (4.3%)
Charlson/Deyo comorbidity score	
0	12,006 (71.1%)
1	1426 (8.4%)
2	297 (1.8%)
Unknown	3162 (18.7%)
Tumor classification	
T1	4991 (29.5%)
T2	6516 (38.6%)
T3	3379 (20%)
T4	2005 (11.9%)
Lymph node classification	
N0	1076 (6.4%)
N1	4076 (24.1%)
N2A	1911 (11.3%)
N2B	5307 (31.4%)
N2C	1232 (7.3%)
N2NOS	2248 (13.3%)
N3	1041 (6.2%)
Treatment	
CCRT	8123 (48.1%)
Surgery plus RT	3519 (20.8%)
Surgery plus CCRT	5249 (31.1%)

Abbreviations: CCRT, concurrent chemoradiation; NOS, not otherwise specified; RT, radiotherapy.
[a] Except for age, all other variables are listed as the total number of patients (no.) as well as the percentage of the entire cohort (%).

TABLE 2. Surgical Margin Status

	Negative Surgical Margins	Positive Surgical Margins[a]	Unknown
Surgery plus CCRT	49.3%	35.2%	15.5%
Surgery plus RT	61.1%	25.9%	13%
Overall	54%	31.5%	14.5%

Abbreviations: CCRT, concurrent chemoradiation; RT, radiotherapy.
[a] Positive surgical margins were reported in a significant minority of patients.

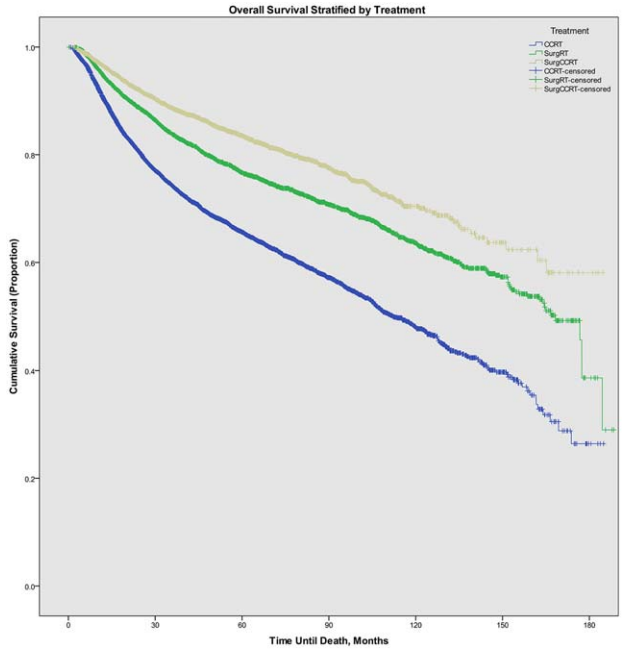

Figure 2. Kaplan-Meier overall survival curves stratified by treatment. This graph represents the entire study cohort of 16,891 patients. Treatment with surgery plus concurrent chemoradiation (SurgCCRT) was found to be associated with the greatest overall survival, followed by surgery plus radiotherapy (SurgRT) and CCRT (3-year OS rates of 88.5%, 84%, and 74.2%, respectively; $P<.001$).

There were 1025 deaths (20.7%) during follow-up with a median follow-up of 43.4 months. Patients who underwent surgery plus CCRT had the greatest 3-year OS rate (90.2%; median survival not reached), followed by those who underwent surgery plus RT (84.9%; median survival of 177.4 months) and patients who underwent CCRT (82.1%; median survival of 161.7 months) ($P<.001$) (Fig. 3A). On multivariable hazards analysis, surgical-based treatments were found to be associated with less risk of death compared with CCRT (surgery plus CCRT: HR, 0.69 [$P<.001$]; surgery + RT: HR, 0.84 [$P = .04$]).

After excluding patients who underwent surgery plus CCRT, a separate propensity score matching was performed and produced a matched cohort of 3992 patients. The overall balance test statistic chi-square was 9.978 with 7 degrees of freedom ($P = .19$), again indicating successful balance based on the input covariates. Figure 3B compares patients treated with CCRT versus those undergoing surgery plus RT. The median OS for the patients who underwent surgery plus RT was 152 months (95% confidence interval [95% CI], 143.8-160.1 months) versus 132 months (95% CI, 121.1-142.4 months) for those receiving CCRT ($P = .002$). On multivariable hazards analysis, treatment with surgery plus RT was associated with less risk of death than treatment with CCRT (HR, 0.85; 95% CI, 0.75-0.95 [$P = .006$]).

DISCUSSION

A major advantage of upfront surgery over definitive CCRT is that surgical pathology can be used to individually tailor treatment, intensifying it when necessary and deintensifying if appropriate. The results of the current study suggest that upfront surgery can allow for targeted

TABLE 3. Univariable and Multivariable Hazards Analysis for Overall Survival[a]

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.04 (1.03-1.04)	<.001	1.02 (1.02-1.02)	<.001
Y of diagnosis	0.95 (0.94-0.95)	<.001	0.96 (0.95-0.97)	<.001
Race				
White	1		1	
Black	2.24 (2.06-2.44)	<.001	1.43 (1.31-1.56)	<.001
Other	0.53 (0.36-0.77)	.001	0.53 (0.37-0.77)	.001
Insurance status				
Private	1		1	
Government	2.71 (2.55-2.89)	<.001	1.94 (1.81-2.08)	<.001
Uninsured	2.28 (2.04-2.54)	<.001	1.85 (1.65-2.06)	<.001
Unknown	1.22 (1.05-1.42)	.01	0.99 (0.85-1.15)	.86
Charlson/Deyo comorbidity score				
0	1		1	
1	1.74 (1.58-1.93)	<.001	1.54 (1.39-1.70)	<.001
2	2.20 (1.82-2.66)	<.001	1.61 (1.33-1.95)	<.001
Unknown	1.63 (1.53-1.75)	<.001	1.08 (0.97-1.20)	.17
Tumor classification				
T1	1		1	
T2	1.59 (1.46-1.73)	<.001	1.34 (1.22-1.46)	<.001
T3	2.67 (2.44-2.92)	<.001	1.86 (1.69-2.06)	<.001
T4	4.36 (3.97-4.78)	<.001	2.72 (2.45-3.01)	<.001
Lymph node classification				
N0	1		1	
N1	0.62 (0.55-0.69)	<.001	1.06 (0.94-1.20)	.31
N2A	0.42 (0.36-0.48)	<.001	0.91 (0.78-1.06)	.23
N2B	0.63 (0.56-0.70)	<.001	1.16 (1.04-1.31)	.01
N2C	1.21 (1.06-1.38)	.005	1.56 (1.37-1.78)	<.001
N2NOS	0.68 (0.60-0.77)	<.001	1.22 (1.07-1.38)	.003
N3	1.31 (1.15-1.50)	<.001	1.85 (1.62-2.12)	<.001
Treatment				
CCRT	1		1	
Surgery plus RT	0.60 (0.56-0.65)	<.001	0.82 (0.76-0.89)	<.001
Surgery plus CCRT	0.43 (0.40-0.47)	<.001	0.68 (0.63-0.74)	<.001

Abbreviations: 95% CI, 95% confidence interval; CCRT, concurrent chemoradiation; HR, hazard ratio; NOS, not otherwise specified; RT, radiotherapy.
[a] Age and year of diagnosis are continuous variables. All other variables are categorical variables.

postoperative therapy, avoiding chemotherapy while still affording better survival. In the current study cohort, approximately 40% of surgical patients avoided chemotherapy. The indication for postoperative chemotherapy in the other 60% of patients was unknown because only 35% of the patients were found to have positive surgical margins and data regarding extracapsular extension were not available for the majority of patients included in this data set.

Discrepancy in clinical and pathologic staging is not uncommon, and can impact prescribed treatment. In a review of 76 patients who underwent TORS, 76% of patients with stage I/II disease and 46% of patients with stage III/IV disease avoided CCRT.[2] Conversely, in the cohort of patients with early-stage disease who would have received RT alone based on clinical staging, 33% had their treatment intensified to postoperative CCRT based on pathologic information. A separate review of 42 patients treated with TORS arrived at similar conclusions, demonstrating that surgical pathologic information changed the stage of disease in 43% of patients. In this study, when comparing the survival data of patients treated with TORS against those of the patients treated with definitive CCRT, the 3-year OS rate was higher among those undergoing surgery, but was not statistically significant (83% vs 57%; $P = .06$).[3] In this retrospective comparison, pretreatment differences in tumor staging were found to exist between the surgical and nonsurgical cohorts, which may be responsible for some of the differences noted with regard to survival.

To the best of our knowledge, there has never been a clinical trial comparing definitive CCRT with upfront surgery followed by tumor-directed adjuvant therapy. The results of the current study suggest that performing upfront surgery followed by RT is not inferior to definitive CCRT, and that some patients experience a survival benefit from the use of surgery plus CCRT. The results of the current study demonstrated that upfront surgery

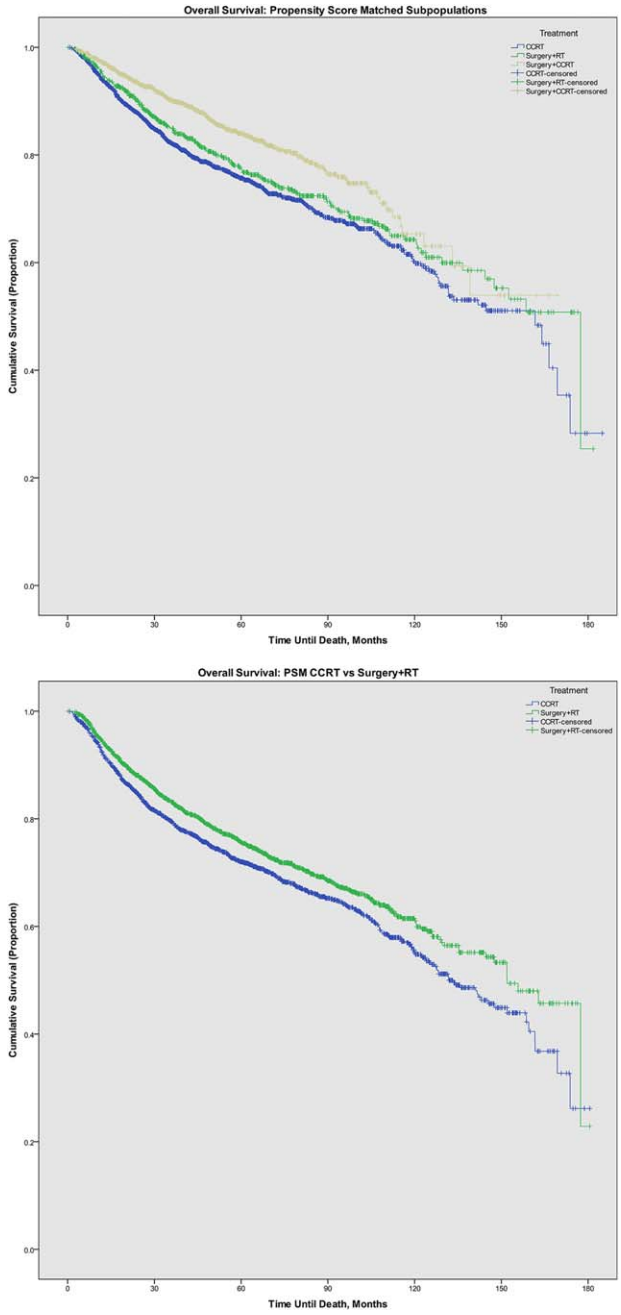

Figure 3. Kaplan-Meier overall survival curves for the propensity score-matched (PSM) cohorts. After PSM, surgical-based treatments continued to be associated with improved overall survival compared with definitive concurrent chemoradiation (CCRT). (A) Comparing all 3 treatment modalities ($P<.001$). (B) Separate PSM cohort comparing only dual-modality treatments ($P = .002$). RT indicates radiotherapy.

followed by CCRT was associated with the greatest OS. Based on these data, one can hypothesize that there are certain patients with advanced stage cancer of the tonsil who benefit from triple-modality therapy. Furthermore, one could theorize that it may be those patients who are negative for human papillomavirus (HPV) and who have a significant smoking history who are known to have the worst prognosis and may require intensified, maximal therapy. These patients have an expected 3-year OS rate of 46.2% if treated with chemoradiotherapy according to the study by Ang et al.[4] This hypothesis is supported by a different NCDB review that demonstrated a survival benefit for HPV-negative patients with oropharyngeal cancer treated with surgery plus CCRT over surgery alone, but a lack of survival benefit for their HPV-positive counterparts.[5] Further investigation is required to determine whether these patients may experience a survival benefit with triple-modality therapy.

Some centers or practitioners are hesitant to offer surgery upfront if they believe that a patient is likely to require CCRT with or without surgery. This philosophy assumes that surgery would be an additional modality with the possibility of increased morbidity and no added survival benefit. The results of the current study suggest that triple-modality therapy may provide a survival benefit for a group of patients.

The addition of chemotherapy to surgery and RT is an accepted treatment escalation paradigm for patients with advanced head and neck cancer. The use of postoperative CCRT increased significantly in 2005 after the European Organization for Research and Treatment of Cancer Trial 22931 and Radiation Therapy Oncology Group (RTOG) 9501 studies and their pooled analysis demonstrated locoregional control and a survival benefit for patients with extracapsular extension (ECE) or positive surgical margins.[6-8] However, other studies have questioned the need for postoperative CCRT in HPV-positive patients with cancer of the oropharynx who are treated with upfront surgery and found to have ECE. The biology of HPV-positive tumors of the oropharynx is very different from that of other smoking-induced and alcohol-induced cancers, and therefore the conclusions drawn from these studies regarding "high-risk head and neck cancer patients" may not be applicable to the current majority of patients with tonsillar/oropharyngeal cancer. Many studies have cited similar survival outcomes between HPV-positive patients with oropharyngeal cancer with ECE who receive postoperative RT alone versus postoperative CCRT.[9-11]

To the best of our knowledge, the only clinical trial to date to investigate the potential benefit of triple-modality therapy in HPV-negative patients with oropharyngeal cancer was closed in 2016 due to lack of accrual (RTOG 1221). In the absence of level 1 data, large-scale databases that include the largest cohorts of patients with

cancer might provide preliminary evidence that could be tested in a randomized clinical trial. Therefore, the current study was undertaken. We limited the study population to the tonsil subsite because of the lower morbidity of tonsillectomy compared with base-of-tongue resection as well as the accessibility of the tonsil subsite.

Although the use of CCRT may be required in some patients, it should be used judiciously. A meta-analysis of 3 clinical trials (RTOG 91-11, 97-03, and 99-14) concluded that severe late toxicity was common (43%) in patients treated with CCRT for advanced stage head and neck cancer.[12] Furthermore, the long-term follow-up to the RTOG 91-11 study demonstrated a significantly higher number of deaths not attributable to laryngeal cancer in the patients treated with CCRT compared with those receiving RT alone.[13] In addition, the 5-year and 10-year OS rates were not found to be significantly different among the 3 cohorts. This suggests that CCRT may have long-term sequelae that contribute to poor long-term health outcomes. Despite these data, patients in the current study who received adjuvant CCRT after surgery were found to have improved survival compared with patients who received CCRT alone or surgery and RT alone. These differences remained after controlling for confounding variables and across propensity score-matched subpopulation analysis. The median survival for the patients treated with surgery plus CCRT was not reached in the current study, with the long-term follow-up encompassing a 14-year period. This is an important point because unlike many other advanced stage cancers of the head and neck, long-term survivorship in patients diagnosed with tonsil cancer is common. To our knowledge, the question of whether patients treated with triple-modality therapy in the current study had different functional outcomes compared with those treated with CCRT or surgery plus RT is unknown, and is a major limitation of the NCDB analysis. Consideration of long-term functional outcomes and the effect additional modalities of treatment have on them becomes increasingly important for these patients who have a relatively good prognosis. The survival curves appear to become more similar at the time of 10-year follow-up. To our knowledge, it is unknown whether this is secondary to the long-term toxic effects of triple-modality therapy, or if this is because of the relatively small number of patients in this cohort who were treated with surgery plus CCRT and had >10 years of follow-up (246 patients; 4%). However, these data suggest that there might be a population of patients with advanced stage cancer of the tonsil who would derive a survival benefit from triple-modality therapy.

The major limitation of the current study is the lack of data available regarding HPV status. HPV status has been shown to be a major prognostic indicator in both surgical and nonsurgical patients.[4,9,14] The year of diagnosis was used as a variable in both the propensity score matching algorithm as well as in the multivariable hazards analysis, which may serve as a surrogate marker for increasing HPV prevalence in the more recent years of the study cohort. To the best of our knowledge, there currently is no indication that patients with HPV-positive tumors are more or less likely to undergo surgical treatment compared with HPV-negative patients. However, if the HPV epidemiology was in fact different between the surgical and nonsurgical treatment cohorts in the current study, that could confound our conclusions. The NCDB began documenting HPV status in 2010, and thus future studies will be able to use this important piece of information in multivariable analysis and propensity score matching. Nevertheless, lack of information regarding HPV status remains an important limitation of the current study.

Another limitation of the current study is the inability to determine why certain patients were selected for certain treatments, thus introducing the possibility of selection bias for the surgical treatment of smaller tumors and nonsurgical treatment for larger tumors. We have tried to minimize this possibility by controlling for comorbidities and tumor and lymph node classification, along with other potential factors in both the multivariable analysis and the propensity score matching algorithm. Although these efforts may limit the potential of selection bias, it cannot be completely eliminated and remains an inherent limitation for comparing survival outcomes in this retrospective review. Furthermore, the NCDB does not include information regarding the toxicities of treatment, swallowing function, or patient quality of life. The treatment of oropharyngeal cancer has a severe impact on these functional outcomes, and many effects are chronic. As stated earlier, severe late toxicity after CCRT is common, reportedly affecting 43% of survivors.[12] In an analysis of 110 patients with advanced stage oropharyngeal cancer (57% of whom had cancer of the tonsil) who were treated with nonsurgical therapy (74% with chemoradiotherapy), approximately 85% of survivors required a modified diet and 38% reported restrictions while eating in public 36 months after treatment.[15] In a multicenter study of 204 patients with oropharyngeal cancer who were treated with transoral laser microsurgery with or without adjuvant therapies (RT or CCRT),

functional outcome swallowing scores of 0 to 2 (representing good swallowing function) were achieved in approximately 90% of patients who received no adjuvant treatment, 88% of patients who received adjuvant RT, and 78.7% of patients who received adjuvant CCRT.[16] Although these data suggest worsening swallowing outcomes with the addition of treatment modalities, to the best of our knowledge there are no studies published to date that have compared these outcomes between surgery plus CCRT versus CCRT alone.

Conclusions

Triple-modality therapy is associated with improved OS compared with definitive CCRT in the treatment of patients with advanced stage cancer of the tonsil. Upfront surgery followed by CCRT was associated with the greatest OS rates. The assumption that surgical treatment will not add a survival benefit if CCRT is needed might not be true. A prospective clinical trial to escalate treatment, such as those currently underway for patients with HPV-positive tumors to deescalate treatment, may need to be reconsidered.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Dylan F. Roden, **David Schreiber**, and **Babak Givi** contributed equally to the conceptualization, methodology, investigation, validation, analysis, and writing of the article. All the authors are responsible for the overall content as guarantors.

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