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Transoral Surgery in HPV-Positive Oropharyngeal Carcinoma: Oncologic Outcomes in the Veterans Affairs System

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Abstract

Objectives: Most transoral robotic surgery (TORS) literature for HPV-positive oropharyngeal squamous cell carcinoma (HPV-OPC) derives from high-volume tertiary-care centers. This study aims to describe long-term recurrence and survival outcomes among Veterans Health Administration patients.

Materials and Methods: Using the US Veterans Affairs database, we identified patients with HPV-OPC treated with TORS between January 2010 and December 2016. Patients were stratified in risk categories: low (0–1 metastatic nodes, negative margins), intermediate (close margins, 2–4 metastatic nodes, lymphovascular or perineural invasion, pT3-pT4 tumor), or high (positive

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margins, extranodal extension (ENE), and/or ≥5 metastatic nodes). Primary outcomes included overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS).

Results: The cohort included 161 patients of which 29 (18%) were low-risk, 45 (28%) intermediate-risk, and 87 (54%) high-risk. ENE was present in 41% of node-positive cases and 24% had positive margins. Median follow-up was 5.6 years (95%CI, 3.0–9.3). The 5-year DSS for low, intermediate, and high-risk groups were: 100%, 90.0% (95%CI, 75.4–96.1%), and 88.7% (78.3–94.2%). Pathologic features associated with poor DSS on univariable analysis included pT3-T4 tumors (HR 3.81, 95%CI, 1.31–11; p=0.01), ≥5 metastatic nodes (HR 3.41, 95%CI, 1.20–11; p=0.02), and ENE (HR 3.53, 95%CI, 1.06–12; p=0.04). Higher 5-year cumulative incidences of recurrence were observed in more advanced tumors (pT3-T4, 33% [95%CI, 14–54%] versus pT1-T2, 13% [95%CI, 8–19%]; p=0.01).

Conclusions: In this nationwide study, patients with HPV-OPC treated with TORS followed by adjuvant therapy at Veterans Affairs Medical Centers demonstrated favorable survival outcomes comparable to those reported in high-volume academic centers and clinical trials.

Lay Summary:

In this nationwide study, patients with HPV+ oropharyngeal carcinoma treated with TORS followed by adjuvant therapy at Veterans Affairs Medical Centers demonstrated favorable survival outcomes comparable to those reported in high-volume academic centers and clinical trials.

Keywords

HPV; Oropharyngeal carcinoma; Transoral surgery; Oncologic outcomes

INTRODUCTION

Human papillomavirus (HPV) represents a common sexually transmitted infection worldwide, and an increasingly important cause of oropharyngeal squamous cell carcinoma (OPC).[1,2] HPV-positive oropharyngeal carcinoma (HPV-OPC) constitutes approximately three-quarters of oropharyngeal cancers, represents the most common HPV-driven malignancy in the United States, and continues to increase in incidence.[2] An important feature of HPV-OPC is that it carries a favorable prognosis compared to HPV-negative OPC.[3] Current National Comprehensive Cancer Network (NCCN) therapeutic guidelines offer high cure rates but often also impart considerable short- and long-term toxicity.[4] In light of these observations, treatment guidelines are shifting toward approaches to balance high cure rates with treatment-related toxicity, and multiple clinical trials are ongoing to evaluate treatment de-intensification with the goal of preserving favorable oncologic outcomes while mitigating toxicity.[5]

Minimally invasive surgical techniques such as transoral robotic surgery (TORS) and, to a lesser extent transoral laser surgery (TLS), have been increasingly applied to HPV-OPC as strategies to reduce the impact of surgical access to decrease morbidity to patients with a generally favorable disease. Decisions on post-operative adjuvant radiotherapy are dictated upon review of pathologic features of the surgical specimen. To date, the majority of TORS outcomes data have been reported from clinical trial settings and single and multi-institution

groups at tertiary care academic institutions. These studies have delineated clinicopathologic risk stratification strategies and adjuvant treatment protocols to optimize patient survival and minimize therapy-associated morbidities.[6] In the tertiary care academic setting, primary resection of resectable HPV-OPC by TORS has been demonstrated to maintain excellent oncologic outcomes, including in cases for which adjuvant radiotherapy may be avoided.[6,7]

Most patients with HPV-OPC who undergo TORS are treated at academic medical centers. A minority (~14%) are treated outside of the academic setting.[8] The treatment patterns and long-term outcomes of HPV-OPC treated with transoral surgery in non-tertiary care or non-academic settings in the United States remains largely unknown. The Veterans Affairs Medical Centers (VAMC) represents a health care setting comprised of 172 medical centers across the United States with regional variation in clinical practice, which may represent a unique patient population compared to that described in high-volume academic centers and clinical trials.[9] While many VAMC facilities are affiliated with academic medical centers, VAMC surgical staff more closely resemble those found in non-academic settings.

The VAMC maintains a centralized medical record system and cancer registry enabling the identification and analysis of specific clinical contexts. Importantly, VAMC medical records overcome limitations of other national hospital-based and epidemiologic databases, which only measure overall survival, by enabling the interrogation of vital oncologic outcomes including incidence of first recurrence, progression-free survival, and disease-specific survival. Taking advantage of these features of the Veterans Health Administration registry, the present study evaluated oncologic outcomes, adjuvant treatment patterns, recurrence rates, and survival in risk-stratified patients with HPV-OPC treated with primary transoral surgery.

METHODS

Data Sources

This study was conducted using data from the Veterans Affairs National Electronic Health Record (VANEHR), Corporate Data Warehouse (CDW), and Veterans Affairs Central Cancer Registry (VACCR) accessed with the VA Informatics and Computing Infrastructure (VINCI). The VACCR conforms with standards set by the North American Association of Central Cancer Registries for detecting and reporting incident cancer cases and treatments. The VA records demographic, clinical and treatment parameters for more than one million veterans treated at 172 medical centers. This study was approved by the San Diego VAMC Institutional Review Board.

Patient cohort and data collection

Patients with biopsy-confirmed p16-positive squamous cell carcinoma of the oropharynx without distant metastatic disease who were treated with either transoral laser or robotic resection of the primary tumor between 2010 and 2016 met inclusion criteria for this study. Using pre-defined oncologic data fields in VINCI, patients were selected for oropharynx anatomic subsites, squamous cell carcinoma histopathology, p16 or HPV-positive tumor status, absence of distant metastasis, and surgical treatment.

Manual patient record review was performed independently (by A.K. & D.C.) and closely reviewed by a fellowship-trained Head and Neck Surgical Oncologist (R.K.O.) to confirm all patients met inclusion criteria for p16-positive and/or HPV-positive tumor status and primary surgical excision. Manual medical document review was employed to verify all data elements including age, sex, race/ethnicity, performance status, cumulative primary exposure to tobacco, surgical margin status (positive, close [defined as < 3 mm], and negative), presence of perineural invasion (PNI), presence of lymphovascular invasion (LVI), presence of extranodal extension (ENE) in patients with pathologic node-positive disease, number of pathologic lymph nodes, adjuvant treatment modality, and radiation dosage. Two percent of patients had unknown margin status and were excluded from analyses related to margin status. Charlson Comorbidity Index (CCI) was calculated using data from one year prior to diagnosis and categories were assigned based on the distribution of scores across the patient cohort.

National Death Index (NDI) data from the US Department of Defense were used to identify date and cause of death. Cause of death was secondarily confirmed with manual review of patient records. Anatomical location and date of recurrence was determined from manual review of patient records. The last day of follow-up was March 11, 2020 (last day of data collection).

The ECOG-ACRIN 3311 (E3311) schema were referenced to guide risk-group categorization.[5] Low-risk subjects were defined as pT1-T2, pN0-N1 and no other adverse features. Intermediate-risk subjects included those with close surgical margins, 2 to 4 pathological lymph nodes, presence of LVI or PNI, and no high-risk features. Of note, pathologic T3 or T4 tumor status was included as an intermediate risk classifier although this was not included as an intermediate risk factor in E3311 because it has broadly been reported to be associated with poor survival.[10] High-risk subjects displayed disease with positive surgical margins (PSM), extranodal extension, and/or greater than 5 lymph pathological nodes.

Study Endpoints

The primary endpoint was disease-specific survival (DSS). Secondary endpoints included incidence of first recurrence, overall survival (OS), progression-free survival (PFS), and disease-unrelated specific survival (DUS). DSS was defined as time from diagnosis to death from oropharyngeal cancer. For DSS, causes of death attributable to non-oropharyngeal cancer etiologies were treated as competing events. OS was determined from the date of diagnosis to the date of death from any cause. DUS was defined as time from diagnosis to death from any cause other than oropharyngeal cancer. PFS was defined as the date of diagnosis to date of first recurrence. Local recurrence was defined by the detection of a histopathologically similar carcinoma at or directly adjacent to the primary site after the completion of curative-intent treatment. Recurrence in the cervical lymph nodes represented regional recurrence and distant recurrence was defined by the detection of a histopathologically similar carcinoma distant to local and regional sites.

Statistical Analysis

Cumulative incidence estimates were used to evaluate first-recurrence across risk groups and were adjusted for the competing risk of death from any cause. Cumulative incidence estimates were used to evaluate death from cancer across risk groups and were adjusted for the competing risk of non-cancer death. This method is similar to the Kaplan-Meier method of censoring patients alive at last follow-up, but instead accounts for patient death before recurrence to avoid overestimating survival rates. We modeled disease-specific survival (DSS) using competing events of cancer versus non-cancer death with a Fine-Gray regression and reported hazard ratios (HR) with 95% confidence interval (CI). We modeled overall survival (OS) using a Cox proportional hazards model. All statistical tests were performed using SAS version 9.4 (SAS Institute Inc.), two-sided tests, and an alpha threshold of $p<0.05$.

RESULTS

Baseline Characteristics

The VHA cohort consisted of 161 patients from a total of 54 VA sites. The majority of patients were White (81%) and male (98%). Median age was 64 years-old (95%CI, 51–81). At the time of presentation, most patients reported a clinically significant smoking history (≥10 pack years: 57%), and were documented to have excellent performance status (ECOG 0 or KPS 100: 56%, Table 1).

A larger proportion of patients presented with primary tumors of the palatine tonsils than the base of tongue (80% vs 20%). Most patients had pT1-pT2 primary tumors (87%) and pN0-pN1 nodal disease (96%). More than one-third of patients had extranodal extension (ENE) (41%) and positive or close surgical margins occurred in 24% and 14%, respectively. Lymphovascular invasion was seen in 22% and perineural invasion in 11% of cases (Table 1).

Application of the E3311 risk group definitions classified 54% of the patients as high-risk, 28% as intermediate-risk, and 18% as low-risk. Primary adverse features contributing to high-risk classification included ENE (present in 66% of high-risk patients), positive margins (44%), and ≥ 5 involved lymph nodes (26%). High-risk patients with ENE were more likely to receive post-operative chemoradiation (CRT) than radiotherapy (RT) alone (81% vs 19%; p=0.01). Intermediate group patients were more likely to receive RT than CRT (64% vs 29%; p=0.005). Low-risk disease patients did not receive adjuvant therapy in 48% of cases, while 34% received RT, and 17% adjuvant CRT (Table 2). Three intermediate-risk (10%) and six high-risk patients (7%) were offered adjuvant treatment but declined treatment. Adjuvant treatment by surgical margin status, ENE, and number of positive nodes are detailed in Table S1.

The number of cases treated with primary surgery increased over time from 39 in 2009–2012, to 122 in 2013–2016. Positive surgical margins (PSM) were less common in later years. From 2009–2014, there were 114 cases with an overall 30% PSM rate (p=0.02) versus 47 cases from 2015–2016 with an overall 5% PSM rate. There were no statistically

significant differences in PSM between pT1-pT2 and pT3-pT4 disease (24% vs 25%; p=0.57). Adverse features by pathological tumor category are shown in Table S2.

Overall and Disease-Specific Survival

The median follow-up time was 5.6 years (95%CI, 3.0–9.3). At the end of the study period, 124 (77%) patients remained alive, 14 (9%) had died from HPV-OPC, and 23 (14%) had died from causes unrelated to HPV-OPC. The respective 2-year and 5-year disease-specific cumulative incidences of mortality were 1.3% (95%CI, 0–3.3%) and 8.6% (95%CI, 4.4–14.4%). The respective 2-year and 5-year all-cause cumulative incidences of mortality were 5.3% (95%CI, 2.5–9.6%) and 21% (95%CI, 15–29%). Across risk categories, the 2-year overall survival (OS) ranged from 90–94%, 5-year OS from 71–88%, 2-year disease-specific survival (DSS) from 97–100%, and 5-year DSS from 89–100% (Table 3). DSS did not significantly differ by risk category (Figures S1A).

Only cumulative primary tobacco exposure was associated with overall survival (HR 2.11, 95%CI, 1.03–4.29; p=0.04). Factors associated with worse DSS included pT3-pT4 category (HR 3.81, 95%CI, 1.31–11; p=0.01), 5 or greater positive lymph nodes (HR 3.41, 95%CI, 1.20–11; p=0.02), ENE (HR 3.53, 95%CI, 1.06–12; p=0.04), and non-White race (HR 2.96, 95%CI, 1.00–8.72; p=0.05) (Figures 1 and S1, Table S3).

Patterns and Outcomes of Recurrence

Twenty-four patients (15%) experienced disease recurrence, with a median time to recurrence of 1.6 years (95%CI, 0.3–5.1) from initial diagnosis. Recurrences occurred locally in 38%, regionally in 33%, and at distant sites in 29% of cases. The respective 5-year cumulative incidences of first recurrence for the low, intermediate, and high-risk categories were 17% (95%CI, 6–33%), 18% (95%CI, 8–30%), and 13% (95%CI, 7–22%, Figure S2), respectively. Advanced pathological tumor category represented the only factor associated with incidence of first recurrence (Figure 2). The 5-year cumulative incidence of distant metastasis with death as a competing event for the low, intermediate, and high-risk categories was 0%, 12% (95%CI, 8–30%), and 8% (95%CI, 4–24%), respectively.

Among the 24 patients who recurred, 14 (54%) died of disease, 5 intermediate-risk and 9 high-risk patients. Death from recurrent disease occurred at a median of 1.3 years (95%CI, 0.3–4.8 years) after recurrence: (Table 4). Twenty-two patients (92%) received salvage treatment: CRT (n=8), RT (n=7), surgery (n=4), and chemotherapy (n=3). Of the 9 patients with intermediate or high-risk disease who declined adjuvant therapy, 2 recurred regionally and 1 succumbed to disease.

Higher 5-year cumulative incidences of recurrence were observed in patients with more advanced primary tumors (pT3-T4, 33% [95%CI, 14–54%] versus pT1-T2, 13% [95%CI, 8–19%]; p=0.01). Rates of recurrence with respect to adverse features are shown for all patients (Figures 2 and S2) and for high-risk patients (Figure S3).

DISCUSSION

Herein, we present a large multi-institutional cohort of patients with HPV-OPC treated with primary transoral surgery. Existing literature describing oncologic outcomes for HPV-OPC patients is mainly derived from high volume centers and clinical trials with stringent surgeon credentialing requirements.[6,11] Although oncologic outcome data for patients with HPV-OPC is available in other national hospital-based and epidemiological databases; these datasets only offer insight on overall survival.[8] Using the novel Veterans Affairs Informatics and Computing Infrastructure (VINCI) data source, we provide insight into treatment patterns and oncologic outcomes in patients with HPV-OPC treated with upfront surgery across centers in the United States. VAMC maintain considerable regional variation in clinical practice that may represent a patient population unique to high-volume academic centers and clinical trials.

We demonstrate favorable oncologic outcomes for patients with HPV-OPC treated with upfront transoral surgery in VAMC settings. Specifically, we found that two- and five-year OS and DSS in patients who received transoral surgery for HPV-OPC at VAMC settings were similar to rates reported in studies from academic medical centers.[6,7,11,12] Our study offers further support for the efficacy of upfront transoral surgery in HPV-OPC, particularly in low-risk patients who displayed a 5-year DSS rate of 100%, despite 50% of patients who received adjuvant radiotherapy.

Adverse pathological features in HPV-OPC have been associated with worse outcomes.[13] However, the prognostic role of adverse features in HPV-associated disease remains unclear.[14,15] We demonstrate that ENE was associated with 3.5-fold greater risk of disease-specific death (HR=3.53), despite approximately 80% of these patients receiving adjuvant chemoradiotherapy. Patients presenting with 5 or more pathological lymph nodes also had a nearly 3.5-fold risk of disease-specific mortality (HR=3.41), consistent with its classification as a high-risk feature.[4] While transoral surgical resection is not commonly performed in patients with T3 or T4 disease (<5%),[8] our cohort included 23 T3/T4 cases (13%). We found that advanced primary tumor category was associated with significantly worse DSS (HR=3.81) than pT1 or pT2 disease, underscoring the need for careful patient evaluation selection prior to offering transoral surgery.

The rate of positive surgical margins (PSM) in OPC is decreasing nationally.[16,17] The PSM rate in our cohort was 24%. This high-rate in our study population could be derived in part from heterogeneity in surgeon experience. The PSM rate did diminish from 30% in 2009–2014 to 5% in 2015–2016, suggesting an improvement in surgical technique or patient selection. High-volume academic centers have reported positive surgical margin rates in patients treated with transoral surgery of approximately 10%,[18] meanwhile National Cancer Database (NCDB) studies have observed higher rates at approximately 16–20%.[19,20] A study of 2,661 patients treated with transoral surgery found that positive margins were present in 15.3% at academic centers and 24.5% at nonacademic centers.[16] At 161 cases over 6 years between 54 VA sites, the VAMC may be considered low-volume centers, and as such, shows similar positive margin rates as low-volume centers reported in the literature. With regard to extranodal extension status, in our cohort 41% were positive for ENE,

consistent with an NCDB analysis reporting 44% ENE rate in HPV-OPC.[13]Interestingly, we did not find an association between positive surgical margins and DSS. Similarly, a retrospective analysis of 106 patients with surgically-treated HPV-OPC at a quaternary cancer center demonstrated that margin status was not associated with worse 5-year DSS (p=0.592).[21]

In this cohort, recurrence in the low-risk group was not uncommon (17%), but recurrent disease in these patients tended to occur locally. Consistent with reports from high-volume academic centers many of these patients underwent successful salvage therapy.[22–24] Furthermore, no low-risk patients died of disease during the study follow-up period. Alternatively, patients with intermediate and high-risk disease displayed recurrence rates between 13 and 18%, and of those who recurred, 74% died of cancer. This reflects the need for better systemic treatments for recurrent HPV-OPC in the setting of intermediate or high-risk features.[25,26] Nonetheless, survival outcomes were reassuring in our cohort despite having a majority of patients classified as high-risk.

Deintensification therapy is under intensive investigation for HPV-OPC.[27] E3311 showed that treatment de-intensification after TORS was associated with favorable outcomes and quality-of-life 35 months postoperatively.[11] Indeed, 2-year OS in low-risk patients was 96–100% irrespective of treatment arm or risk. However, patients selected for participation in clinical trials have been reported to display better performance status and younger age than patients treated in clinical practice.[28] Nevertheless, our cohort showed 2-year OS of 96.6%, 88.9%, and 94.2% for patients with low, intermediate, and high-risk disease, respectively. Furthermore, we show favorable 5-year DSS of 100.0%, 90.0%, and 88.7% in patients with low, intermediate, and high-risk disease. These findings provide valuable oncologic outcomes data for and suggest that outcomes remain favorable for patients treated in non-trial settings.[29,30]

Limitations to our study include its retrospective design and lack of standardized follow-up protocols. In earlier medical records within the Veterans Affairs National Electronic Health Record (VANEHR), p16 status was recorded less frequently, and the total number of patients with p16-positive tumors in this cohort is likely underestimated. Although p16-positivity and HPV-positivity are not equivalent, previous studies have demonstrated comparable survival rates using either p16 or HPV status for risk stratification in OPSCC, thus p16 was used in this study as an appropriate surrogate for HPV status.

Although the VHA centers included in our study had low individual case volumes throughout the study period, a decline in the PSM rate was observed over time, suggesting longitudinal improvements in surgical technique, but our analysis is unable to account for the case-volume experience of individual surgeons. Nonetheless, this study included detailed medical records from patients with HPV-OPC treated and managed at more than 50 VAMCs across the United States.

The median follow-up time for our patients was close to 6 years, which is longer than other similar studies, and included data enabling the ascertainment of DSS and recurrence patterns. More than 98% of our cohort was male and 81% were white. Although this is

reflective of higher HPV-OPC disease prevalence in males and of demographics of the VA patient population, this white race and male predominance may limit the generalizability of our results to female and non-white patients, which represent growing demographics affected by HPV-OPC.[31] Despite these observations, the patients in our study are on average older, more racially diverse, have significant smoking histories, more comorbidities, and worse performance status than may be seen in clinical trial cohorts. Thus, the findings of this study may more accurately reflect outcomes outside of clinical trial settings as well as community practices.

CONCLUSION

In this study, patients with HPV-OPC treated with upfront transoral surgery in VAMC had favorable oncologic outcomes. These findings are comparable to oncological outcomes reported from high-volume academic centers and suggest that the improved outcomes observed in primary TORS for HPV-OPC may suitably represent outcomes observed in unique cohorts compared to those studied at high volume academic centers or in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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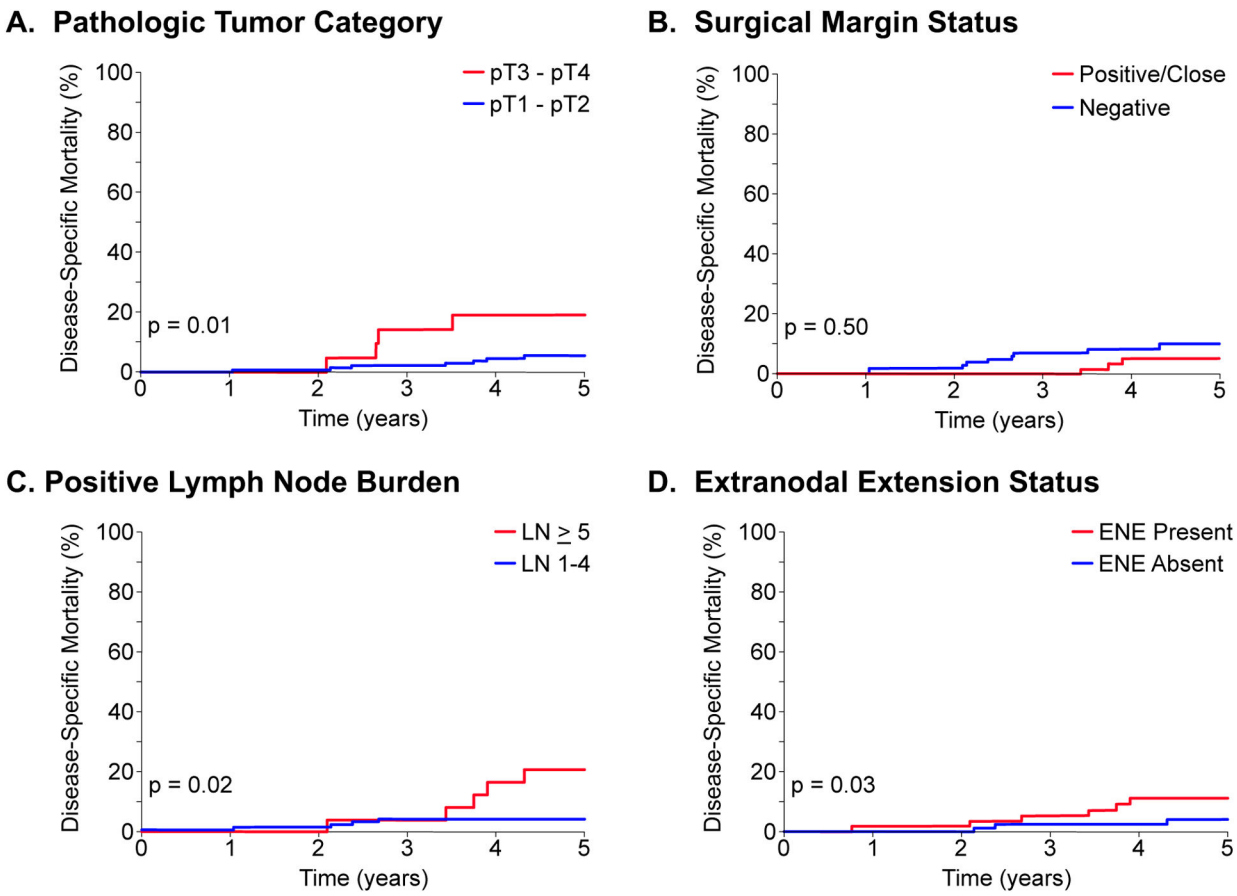
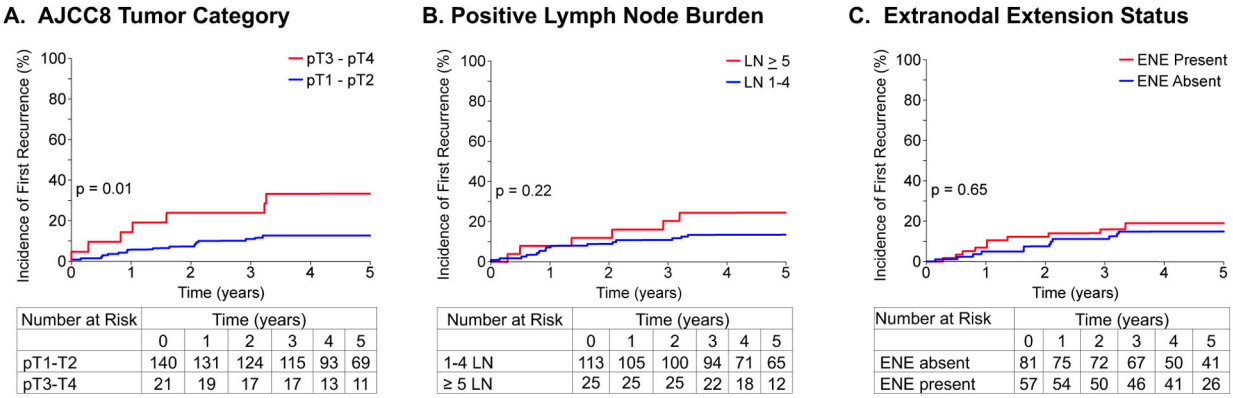


Figure 1.

Disease-Specific Mortality by A) Pathologic Tumor Category, B) Surgical Margin Status, C) Positive Lymph Node Burden, and D) Extranodal Extension Status



Number at Risk	Time (years)					
	0	1	2	3	4	5
pT1-T2	140	131	124	115	93	69
pT3-T4	21	19	17	17	13	11

Number at Risk	Time (years)					
	0	1	2	3	4	5
1-4 LN	113	105	100	94	71	65
≥ 5 LN	25	25	25	22	18	12

Number at Risk	Time (years)					
	0	1	2	3	4	5
ENE absent	81	75	72	67	50	41
ENE present	57	54	50	46	41	26

Figure 2.

Incidence of First Recurrence by A) Pathologic Tumor Category, B) Positive Lymph Node Burden, and C) Extranodal Extension Status

Table 1:

Baseline Characteristics

Variable	Categories	Total, n (%)
Number of patients	continuous	161
Age (median, 95% CI)	continuous	64 (51–81)
Age Groups	≤ 55	31 (19)
	56 – 60	26 (16)
	61 – 65	46 (29)
	66 – 70	40 (25)
	≥ 71	18 (11)
Sex	Male	157 (98)
	Female	4 (2)
Race	White	131 (81)
	Black	15 (9)
	Other	2 (1)
	Unknown	13 (8)
Performance Status	ECOG 0 or KPS 100	75 (47)
	ECOG ≥ 1 or KPS ≤ 90	60 (37)
	Unknown	26 (16)
Smoking History	≥ 10 pack years	91 (56)
	< 10 pack years	70 (43)
Charlson Comorbidity Index	0	85 (53)
	≥ 1	30 (19)
	Unknown	46 (29)
Primary Tumor Anatomic Subsite	Tonsil	128 (80)
	Base of tongue	33 (20)
AJCC8 Pathologic Tumor Category	1	70 (43)
	2	70 (43)
	3	11 (7)
	4	10 (6)
AJCC8 Pathologic Nodal Category	0	23 (14)
	1	131 (82)
	2 – 3	7 (4)
Number of Positive Lymph Nodes	0	23 (14)
	1	62 (39)
	2 – 4	46 (29)
	≥ 5	25 (16)
	Unknown (LN+)	5 (3)
Surgical Margins	Positive	38 (24)
	Close	23 (14)

Variable	Categories	Total, n (%)
	Negative	97 (60)
	Unknown	3 (2)
Extranodal extension (ENE) *	Yes	57 (41)
	No	81 (59)
Lymphovascular Invasion (LVI)	Yes	36 (22)
	No	77 (48)
	Unknown	48 (30)
Perineural Invasion (PNI)	Yes	18 (11)
	No	104 (65)
	Unknown	40 (25)
Risk Category	Low	29 (18)
	Intermediate	45 (28)
	High	87 (54)
Adjuvant Treatment	None	23 (14)
	RT	61 (38)
	CRT	77 (48)
Year of Diagnosis	2009 – 2012	39 (24)
	2013 – 2016	122 (76)

Abbreviations: ENE, extranodal extension. LVI, lymphovascular invasion. PNI, perineural invasion. AJCC8, American Joint Committee on Cancer, 8th edition Cancer Staging System.

*Solely includes patients with node-positive disease

Table 2.

Adjuvant Treatment and Radiation Dose by Risk Category

		Risk Category			
		Low	**Intermediate**	**High**	***P***
Number of Patients		29	45	87	
Adjuvant Treatment	None	14 (48)	3 (7)	6 (7)	<0.001
	Radiation	10 (34)	29 (64)	22 (25)	
	Chemoradiation	5 (17)	13 (29)	59 (68)	
Radiation Dose	None	14 (48)	3 (5)	6 (7)	<0.001
	50 to 59 Gy	2 (6)	1 (3)	2 (2)	
	60 to 66 Gy	6 (26)	33 (77)	50 (57)	
	67 to 70 Gy	5 (17)	3 (5)	19 (22)	
	Unknown	2 (9)	5 (10)	10 (11)	

Abbreviations: Low-Risk: 0–1 lymph node involved and none of features in intermediate or high-risk categories. Intermediate-risk: close surgical margins, perineural invasion, pT3-T4, lymphovascular invasion and/or 2 to 4 lymph nodes involved and none of the features in high-risk category. High-risk: positive surgical margins, extranodal extension, and/or ≥ 5 lymph nodes involved. Gy, Gray, unit of ionizing radiation dose.

Table 3.

Survival Outcomes by Risk Category

	2-year Survival, % (95% Confidence Interval)		
Outcome	**Low Risk**	**Intermediate Risk**	**High Risk**
Progression-Free Survival	89.7 (71.3–96.5)	77.8 (62.6–87.4)	88.4 (79.5–93.6)
Disease-Specific Survival	100 (100–100)	97.6 (83.9–99.7)	97.6 (90.9–99.4)
Disease-Unrelated Survival	94.3 (79.0–98.5)	91.1 (78.0–96.6)	95.2 (87.8–98.1)
Overall Survival	96.6 (77.9–99.5)	88.9 (75.3–95.2)	94.2 (86.6–97.5)
	5-year Survival, % (95% Confidence Interval)		
Outcome	**Low Risk**	**Intermediate Risk**	**High Risk**
Progression-Free Survival	70.7 (49.4–84.3)	68.2 (52.2–79.9)	75.3 (64.1–88.4)
Disease-Specific Survival	100 (100–100)	90.0 (75.4–96.1)	88.7 (78.3–94.2)
Disease-Unrelated Survival	82.9 (63.1–92.7)	79.4 (62.6–89.3)	88.2 (78.3–93.8)
Overall Survival	87.8 (66.0–96.0)	71.4 (55.0–82.8)	80.1 (69.4–87.5)

Table 4.

Site of First Recurrence and Death from Disease by Risk Category

Risk Category	Site of First Recurrence	n (%)	Died from Disease n (%)
Low n = 29	Local	4 (14)	0 (0)
	Regional	1 (3)	0 (0)
	Distant	0 (0)	0 (0)
Intermediate n = 45	Local	2 (4)	2 (100)
	Regional	3 (7)	1 (33)
	Distant	3 (7)	2 (67)
High n = 87	Local	3 (3)	2 (67)
	Regional	4 (5)	3 (75)
	Distant	4 (5)	4 (100)