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Transoral robotic surgery and neck dissection for HPV-positive oropharyngeal carcinoma: Importance of nodal count in survival

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ABSTRACT

Background: In this study we determine the survival in patients with HPV-positive oropharyngeal carcinoma treated with transoral robotic surgery (TORS), neck dissection and risk-adapted adjuvant therapy.

Methods: We retrospectively identified 122 patients with HPV-positive oropharyngeal carcinoma treated with TORS and neck dissection between 2011 and 2018. Survival probability was calculated. We determined the effect of the type of neck dissection performed (modified radical neck dissection-MRND vs. selective neck dissection - SND), extranodal extension (ENE), margin status, and presence of ≥ 5 metastatic nodes on survival.

Results: Our patient population had a five-year overall survival of 91.0% (95% C.I. 85–97%). The five-year probability of recurrence or cancer-associated death was 0.0977 (95% C.I. 0.0927–0.1027). The five-year probability of cancer-associated death was 0.0528 (95% C.I. 0.048–0.0570). All patients who died of their disease had distant metastasis. Our PEG dependence rate was 0%. Patients with ENE and positive margins who underwent adjuvant chemoradiation did not have worse survival. Presence of ≥ 5 metastatic nodes portended worse survival after controlling for age, positive ENE and margins. Low yield (< 18 nodes) on neck dissection worsened DFS on multivariable analysis. Furthermore, patients who underwent SND did not have worse OS than those who underwent MRND.

Conclusion: Our study demonstrates that surgery could be simplified by performing TORS with SND rather than MRND. The one true poor prognostic factor in HPV-positive oropharyngeal carcinoma patients who undergo surgery is high nodal burden. Patients with high nodal burden are much more likely to die from their disease.

Introduction

Human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (SCC) comprises over 70% of newly diagnosed oropharyngeal carcinoma cases [1]. Treatment for oropharyngeal SCC includes surgical resection and neck dissection followed by risk-adapted adjuvant therapy, or definitive chemoradiation. In numerous prospective and retrospective studies over the past ten years, researchers have shown that patients with HPV-positive oropharyngeal carcinoma have a higher cure rate than those with HPV-negative disease, regardless of treatment modality [2–5]. The challenge then became to devise treatment strategies that could mitigate morbidity, while not compromising survival outcomes. Transoral robotic surgery (TORS) has been widely adapted as a surgical strategy to "de-intensify" treatment. Since 2011, our group has performed TORS and neck dissection as the primary treatment for patients with surgically resectable oropharyngeal SCC. This study represents our long-term experience on using TORS in HPV-positive oropharyngeal SCC.

The purpose of this study was to determine oncologic outcomes, as well as risk factors that could influence these outcomes. With a cohort

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of 122 patients, we specifically investigated the effect of the type of neck dissection performed (*i.e.,* modified radical neck dissection vs. selective neck dissection) on survival outcomes. Furthermore we determined the effect of extranodal extension (ENE), margin status, and number of metastatic nodes on survival. We found that the most important predictor of survival was high nodal burden (*i.e.,* having ≥ 5 metastatic nodes). ENE and margin status did not portend a worse prognosis in our group of HPV-positive oropharyngeal SCC patients, presumably due to adjuvant chemoradiation. Lastly, while MRND had the benefit of identifying occult metastasis in levels I and V, patients who underwent MRND had worse survival than patients who underwent SND, after controlling for all other disease characteristics between the two groups.

Methods

Patient selection

The patients within this study were selected from an existing head and neck squamous cell carcinoma (HNSCC) database; collection of clinical data for this database was approved by the Institutional Review Board at Providence Health and Services. All patients who underwent TORS for HPV-positive (identified by p16 status) oropharyngeal carcinoma between April 2010 and September 2018 were included.

Patients had previously untreated, resectable oropharyngeal squamous cell carcinoma. Contraindications were similar to those outlined in the Weinstein *et al.* study, which included distant metastasis, unresectable regional disease (*i.e.,* unresectable lymph nodes), deep invasion of the tissues lateral to the constrictor muscles and prevertebral fascia, and trismus [6]. The surgical approach of TORS for oropharyngectomy were previously described [7,8]. The *da Vinci* Surgical System was used in all cases. After the main specimen was resected and inspected, frozen margins were obtained in the circumferential mucosa and deep margins as necessary. Patients underwent either a modified radical neck dissection (MRND) or a selective neck dissection (SND, levels II, III and IV) with ligation of the lingual and facial artery. The indications for postoperative radiotherapy were previously established in randomized clinical trials [9,10], and included presence of perineural invasion (PNI), lymphovascular invasion (LVI), two or more metastatic lymph nodes, or T4 disease. The indications for concurrent chemoradiation included margin-positive disease and presence of ENE.

Those undergoing radiation therapy were treated with IMRT with either step-and-shoot or VMAT delivery, with simultaneous integrated boost technique, preceded by conebeam localization. Patients were immobilized in a thermoplastic Type–S mask with custom head holders (Civco, Orange City, IA). Planning CT scans (Philips Brilliance, Andover, MA), were performed with or without contrast at the treating radiation oncologist's discretion. The target volumes were contoured by the treating physician, and all contours were reviewed by a second physician. Dose constraints from previous RTOG studies were followed, and since 2010, QUANTEC guidelines were followed [11].The resected primary site received 60 Gy in 2 Gy per fraction for negative margins, and 64–66 Gy for positive margins. The ipsilateral and contralateral neck received 60 Gy if the nodes were involved, with a boost volume of 64–66 Gy if there was positive margin or ENE. The necks received 54 Gy if uninvolved.

Data collection

We collected the following information from the chart review: patient demographics, staging, adjuvant treatment and percutaneous gastrostomy tube (PEG) dependence. Clinical and pathologic stage were recorded based on the American Joint Committee on Cancer (AJCC) Eighth Edition Staging Manual [12].

Data interpretation

Patient characteristics between treatment groups were compared using the Fisher exact test for categorical, and *t* test or nonparametric Wilcoxon rank-sum test for continuous variables. Overall survival (OS) endpoint was the time of surgery to time of any cause of death. Disease-specific survival (DSS) endpoint was the time of surgery to time of death from HNSCC. Disease-free survival (DFS) endpoint was the time of surgery to the time of disease recurrence/metastasis or death from HNSCC. Kaplan-Meier method with log-rank test was utilized to compare OS between SND and MRND. Multivariable survival analysis was performed to determine the association all study variables with OS using Cox-proportional model with Firth's penalized likelihood, which is an alternative to Cox's regression model with a more precise estimation of parameters for small samples with substantial censoring of survival times [13]. Cumulative incidence functions (CIF) were used to compare MRND and SND groups using the function "cuminc" in R package "cmprsk", and competing risk regression analysis was used to determine the association of the study variables with DFS and DSS, taking the competing risk of death from other causes (3 cases) into account, using function "crr" in R package "cmprsk". To compare OS, DFS and DSS between two neck dissection groups, we further performed propensity matching analysis to minimize selection bias and confounding effects from nonrandomized assignment between two groups. Statistical analyses were performed using R software, version 3.6.0 (R Core Team).

Results

Patient demographics

We identified 122 patients with HPV-positive oropharyngeal carcinoma who underwent TORS. Table 1 reports the pertinent characteristics of these 122 patients. The mean age was 61.7, with 91.8% males. The majority of patients did not report significant alcohol or tobacco consumption—82.8% of patients consumed 4 or fewer alcoholic drinks daily, 50.8% of patients were nonsmokers, and 10.7% of patients had a 10 or fewer pack year smoking history.

When patients were grouped by clinical stage, 93.4% of patients had T0, T1 or T2 tumors, and 96.7% patients were staged as N0 or N1, demonstrating that we had selected patients with early stage disease for TORS. Pathologic tumor staging correlated well with clinical staging, with only 11 patients up-staged based on their pathologic stage, either from N0 to N1, or N1 to N2 regional metastasis staging.

Perioperative complications and need for tracheostomy or PEG were examined. There were no perioperative deaths. Four patients (3.3%) underwent a tracheostomy at the time of TORS- all in 2011 at the beginning of our experience- and all were quickly decannulated. Four patients (3.3%) were readmitted to the hospital because of relatively minor bleeding, which occurred between 1 and 4 weeks postoperatively, one of whom required a return to the operating room for vessel ligation/cauterization (0.8%). PEG dependence was defined in previously published studies [14–16] as the need for enteral feeds one year after treatment. Thirteen patients (11%) required a short-term PEG. However our PEG dependence rate at one year was 0%.

Pathologic features

Table 1 details the pathologic features of our study population. 14.8% of patients had positive PNI and 20.5% of patients had positive LVI. ENE status in the neck specimen was as follows: 5.4% of patients had ENE ≤ 1 mm, 42.6% (52/122) of patients had ENE > 1 mm, with the rest of the patients having no ENE. Of the 52 patients with ENE > 1 mm, 44 (84.6%) underwent adjuvant chemoradiation. We also examined margin status; 9 (7.4%) patients had positive margins on initial resection. Of these patients, 8 are currently free of disease after

Table 1
Patient and Tumor Characteristics.

Variable	Stratification	Mean value or number of patients	Percentage
Age (years)	–	61.7	–
Sex	Male	112	91.8
	Female	10	8.2
Median follow up (years)		4.3	
Primary site	Palatine tonsil	59	
	Base of tongue	53	
	Multiple sites	2	
	Glossotonsillar sulcus/ pharyneal wall	2	
	Unknown	5	
Alcohol use	≤4 drinks/day	101	82.8
	> 4 drinks/day	21	17.2
Tobacco use	Nonsmoker	62	50.8
	≤10 pack year	13	10.7
	> 10 pack year	47	38.5
cT stage	T0	5	4.1
	T1	63	51.6
	T2	46	37.7
	T3	8	6.6
cN stage	N0	14	11.5
	N1	104	85.2
	N2	4	3.3
pT stage	T0	5	4.1
	T1	63	51.6
	T2	46	37.7
	T3	8	6.6
pN stage	N0	13	11.5
	N1	94	77
	N2	15	11.5
Pathologic stage	I	102	85.2
	II	20	14.8
Mortality from any cause	No	113	92.6
	Yes	9	7.4
Mortality from HNSCC only	No	116	95.1
	Yes	6	4.9
Recurrence/mortality from HNSCC	No	109	89.3
	Yes	13	10.7
Margin	Negative	113	92.6
	Positive	9	7.4
Perineural invasion	Absent	104	85.2
	Present	18	14.8
Lymphovascular invasion	Absent	97	79.5
	Present	25	20.5
Extranodal extension	Absent	65	53.3
	Present ≤ 1 mm	5	4.1
	Present > 1 mm	52	42.6
Nodal metastasis (no. of patients/total)	Level IA	0/52	0
	Level IB	2/52	3.8
	Level IIA	106/122	86.9
	Level IIB	11/122	9
	Level III	26/122	21.3
	Level IV	7/122	5.7
	Level V	2/52	3.8
Size of largest node (mm)		32.4 ± 14 (4–70)	
Mean no. of metastatic nodes		2.6 ± 2 (1–11)	

adjuvant RT, chemoRT, or re-resection. One patient developed brain metastasis 18 months after TORS. The clinical course for this patient is described below. There were 8 patients with close margins (*i.e.,* final margins ≤ 1 mm), who are all alive, free of disease. Five of these patients also had positive ENE and underwent chemoradiation. Two of the three remaining patients underwent adjuvant radiation.

Survival patterns

Five-year OS was calculated using Kaplan-Meier method with log-rank test (Fig. 1). To determine DFS and DSS, we performed cumulative incidence function calculations to account for the competing risk of death from causes other than cancer. We used this stringent analysis because death in our study population was a rare event, with 6 patients dying of HNSCC and 3 dying of other causes. The five-year probability of recurrence or death from HNSCC was 0.0977 (95% confidence interval 0.0927–0.1027); in other words, probability of disease-free survival was 0.9023. The five-year probability of death from HNSCC was 0.0528 (95% C.I. 0.0486–0.0570).

Seven patients developed locoregional recurrence or distant metastasis and are still alive. The clinical course for these 7 patients are as follows. Three patients had locoregional recurrence, were salvaged with chemoradiation and are currently free of disease. One patient had a recurrence at 7 months and one had a second primary at 7 years after initial TORS; these two patients were salvaged with TORS and are free of disease. One patient with pT1, pN1 BOT disease, positive margins and ENE on pathology developed brain metastasis 18 months after initial surgery. This patient underwent gamma knife, nivolumab, and is currently living with disease. One patient underwent TORS, SND and adjuvant RT for pT2, pN1 palatine tonsil SCC. He developed multiple bilateral pulmonary metastases 20 months after surgery, initially treated with surgical cytoreduction followed by nivolumab and stereotactic body radiation therapy (SBRT). He was transitioned to carboplatin and 5-fluorouracil while continuing nivolumab. He had a partial response to treatment. He was then enrolled in adoptive cell transfer therapy with tumor infiltrating lymphocytes harvested from the right upper lobe. His most recent imaging showed a 67% decrease in the largest metastatic nodule.

Disease outcome of triple modality treatment patients

We examined patients with high-risk features (*i.e.,* ENE and positive margins) who required adjuvant chemoradiation to determine if there was a difference in disease outcome. We had particular interest in this group of patients who underwent surgery and chemoradiation, because while they did not benefit from TORS as a method of de-escalating treatment, we wanted to determine whether triple modality treatment provided a survival benefit in these patients. The most common indication for adjuvant chemoradiation in our study was presence of ENE > 1 mm. 84.6% (44/52) of patients with ENE > 1 mm underwent adjuvant chemoradiation. On univariate and multivariable analysis, DSS was equivalent between patients with and without ENE, suggesting efficacy of the addition of adjuvant treatment in patients with ENE (Table 2; **Fig. S1**). When we considered margins as an independent factor, presence of positive margins significantly reduced DSS ($p = 0.03$); however, statistical significance was not maintained on multivariable analysis. Similarly, univariate, but not multivariable analysis, showed an association of margin status with DFS ($p = 0.04$ and NS, respectively) (**Table S1**; **Fig. S2**). Similarly, margin status did not significantly impact OS on multivariable analysis in our group of patients who were treated with adjuvant chemoradiation for positive margins (**Table S2**).

In looking at patients in the triple modality group, we also saw that we had more patients who underwent triple modality therapy earlier on in the study. We divided the patients up in two groups, those who were treated between 2011 and 2014 and those treated between 2015 and 2018. When we compared rates of adjuvant chemoradiation between patients treated in 2011–2014 and 2015–2018, patients in the 2011–2014 group were much more likely to receive adjuvant chemoradiation (Fig. 2**A**, $p = 0.0016$, Chi square test). Of the 51 patients in the 2011–2014 group, 28 received adjuvant chemoradiation (55%) and 16 received adjuvant radiation (31%). Of the 71 patients in the 2015–2018 group, 19 received adjuvant chemoradiation (27%) and 31 received adjuvant radiation (44%). This shift in practice toward de-escalating treatment is explained by the more selective identification of surgical candidates with increasing robotic experience.

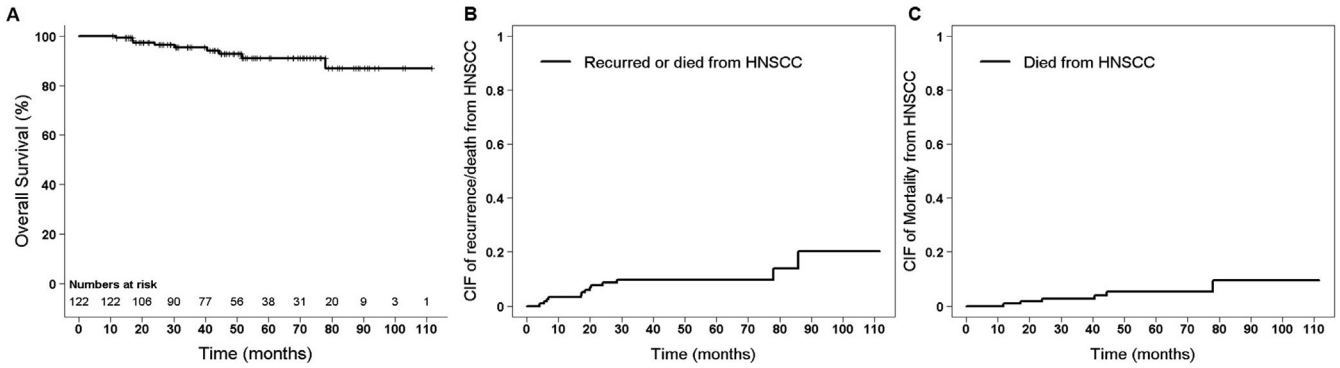

Fig. 1. Survival patterns. (A) The Kaplan Maier survival curve represents the five-year overall survival. **(B)** Cumulative incidence function for recurrence or death from HNSCC is depicted, with a five-year probability of 0.0977 (95% C.I. 0.0927–0.1027). **(C)** The five-year probability of death from HNSCC is 0.0528 (95% C.I. 0.0486–0.0570).

Nodal yield and number of metastatic nodes associated with survival

We looked at neck metastasis based on nodal level to determine if involved nodal level affected disease outcome. Of all the patients with neck disease, the metastatic nodes were in level IIa 86.9% of the time, level IIb 9% of the time, level III 21.3% of the time, and level IV 5.7% of the time (Table 1; Fig. 2**B**). 66 of the 122 total patients had more than one metastatic node in their neck dissection. To calculate the risk of occult level I or V metastasis, we determined the relative risk of level I or V involvement on MRND after a negative presurgical staging evaluation (*i.e.,* based on clinical exam and radiographic findings). Patients were stratified by the number of nodes involved on presurgical clinical staging. Patients with 2 or more metastatic nodes on clinical staging were more likely to have level I or V metastasis compared to patients who had ≤ 1 node on clinical exam (relative risk 2.42, 95% C.I. 1.18–3.28) (Fig. 2**C**). However, the overall incidence of level I/V involvement was < 5%, and did not associate with survival in our study population.

We next determined whether the number of metastatic nodes affected survival. The AJCC 8th edition staging system highlights nodal count as a significant determinant of survival in HPV-positive oropharyngeal carcinoma patients who undergo surgery. In our own study population, 15 patients had pathologic N2 staging with ≥ 5 nodes; 3 of these patients died of distant metastasis. 107 patients had N0 or N1 staging; 3 of the patients in this group died of distant metastasis. 11 of the 15 patients with N2 staging underwent adjuvant

Table 2
Independent predictors of disease-specific survival (DSS) using competing risk regression.

	Univariate Analysis				Multivariable Analysis			
	SHR*	Lower 95% CI	Upper 95% CI	p-value	SHR*	Lower 95% CI	Upper 95% CI	p-value
Age, years	1.12	1.02	1.23	**0.02**	1.12	0.98	1.29	0.11
Tobacco pack years								
Non-smoker								
≤10	6.67	0.90	49.44	0.06				
> 10	1.44	0.20	10.39	0.72				
EtOH (> 4 drinks/day)								
No								
Yes	1.96	0.31	12.30	0.47	1.24	0.68	2.26	0.48
8th pT								
< 2								
≥2	2.53	0.47	13.49	0.28	1.24	0.68	2.26	0.48
8th pN								
N0/N1 (positive nodes < 5)								
N2 (positive node ≥ 5)	6.94	1.59	30.19	**0.01**	0.8	0.09	7.02	0.84
Margin								
Negative								
Positive	5.62	1.23	25.67	**0.03**	0.9	0.08	10.03	0.93
ENE status								
Positive								
Negative	0.17	0.02	1.45	0.11	0.16	0.01	2.78	0.21
Number of nodes examined								
0–17								
18–75	0.27	0.05	1.44	0.13	0.14	0.02	1.21	0.07
PNI perineural invasion								
Present								
Absent	0.16	0.03	0.76	**0.02**	0.11	0.01	1.47	0.10
LVI lymphovascular invasion								
Absent								
Present	1.81	0.34	9.53	0.48	3.6	0.35	36.93	0.28
PEG								
No								
Yes	1.42	0.14	14.01	0.76				

Multivariable analysis includes the following variables: age, pT, pN, margin, ENE, number of nodes examined, PNI, LVI.
* Subdistribution hazard ratio.

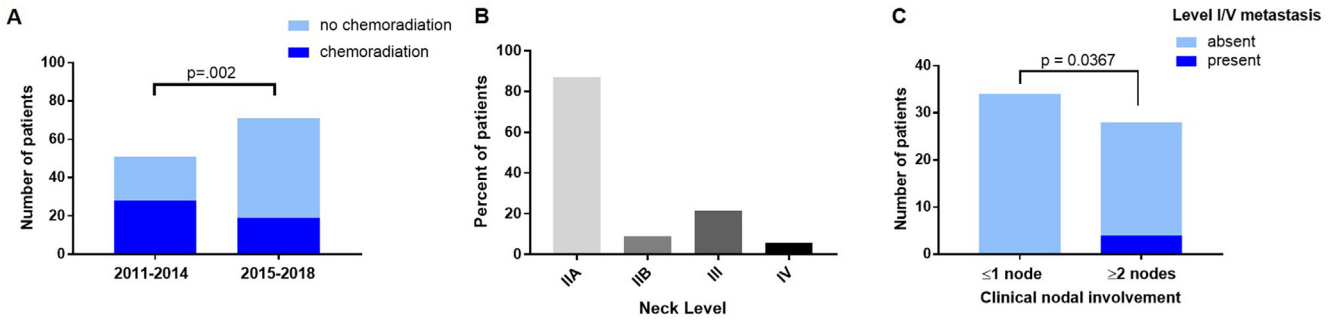

Fig. 2. (A) Differences in adjuvant treatment during the study period. Patients treated between 2011 and 2014 were much more likely to receive adjuvant chemoradiation than patients treated between 2015 and 2018 (Fisher's exact test, p = 0.002). **(B) Neck metastasis by level**. Of the patients with neck disease, metastatic nodes were in level IIa 86.9% of the time, level IIb 9% of the time, level III 21.3% of the time, and level IV 5.7% of the time. **(C) Risk of occult (level I/V) metastasis was higher if a patient had multiple metastatic nodes on clinical exam.** The relative risk of a patient having level I/V metastasis if the initial clinical assessment showed involvement of ≥ 2 nodes was 2.42 (95% CI 1.18–3.28) compared to a patient with ≤ 1 node. Patients with ≥ 2 metastatic nodes on clinical exam were significantly more likely to have level I/V metastasis (p = 0.0367, Fisher's exact test).

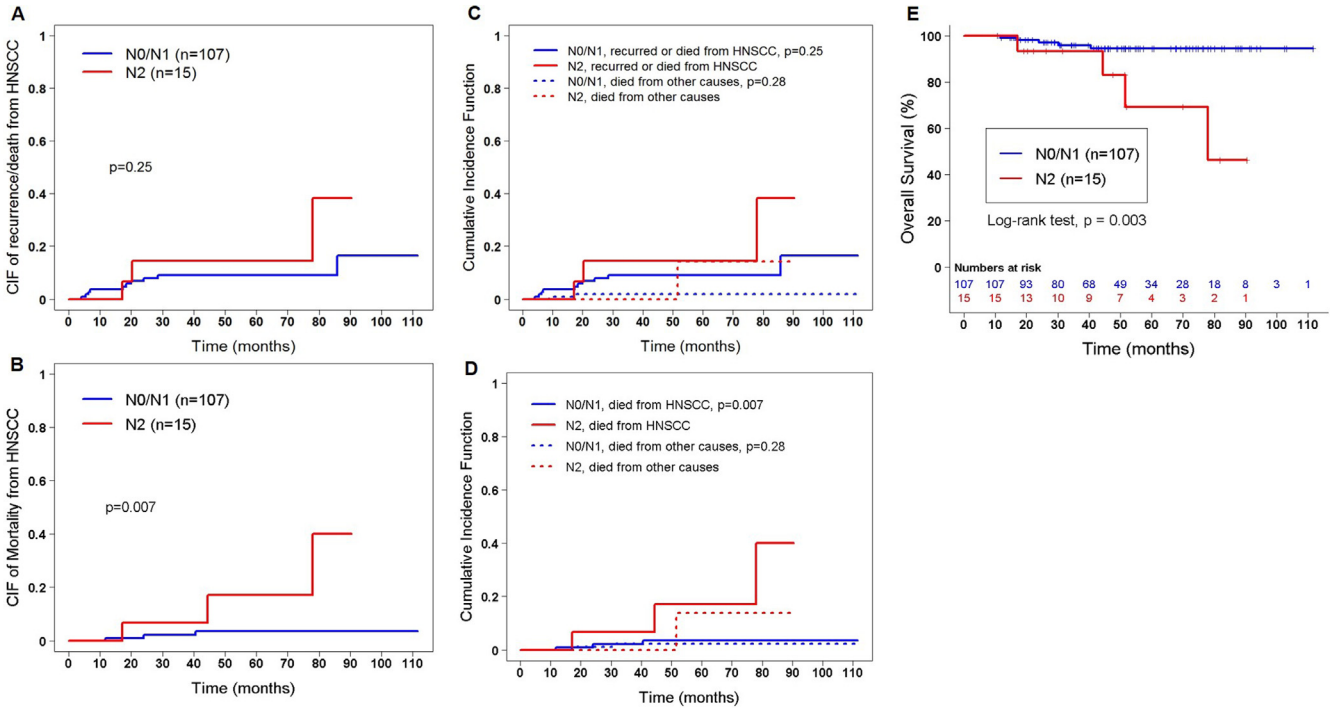

Fig. 3. High nodal burden portended worse survival. (A) Patients were divided by their N status into either N0/1 (n = 107) or N2 (n = 15). There was no difference in risk of DFS between the two groups. **(B)** However, N2 status resulted in a significantly higher chance of dying from HSNCC, with 5-year probability of death being 0.1704 (95% CI 0.1492–0.1916) for N2 disease and 0.0346 (95% CI 0.0311, 0.0382) for N0/1 disease. **(C-E)** While there was no difference in the risk of death from causes other than HNSCC, patients in the N2 group had significantly worse OS than patients in the N0/1 group.

chemoradiation, while the remaining 4 patients underwent adjuvant radiation. We determined the cumulative incidence function (CIF) of recurrence or death from HNSCC in patients with N0/1 disease vs. N2 disease. While patients experienced recurrence in similar proportions, patients with N2 disease were much more likely to die than patients with N0/1 disease (*i.e.,* worse DSS, p = 0.007; Fig. 3**A-B**; worse OS, p = 0.003, Fig. 3**C-E**). In a multivariable analysis that included pN stage, ENE status, margin status, and age, OS was still significantly higher in patients with N0/1 disease than those with N2 disease (p = 0.04). However, when all clinical and pathologic factors were included in the multivariable analysis (pT, pN, ENE, margin, PNI, LVI, number of nodes in neck dissection, and age) the statistical difference in survival was not preserved, as small sample size was a limitation to our analysis.

We compared patients with adequate nodal yield (≥18 nodes) on neck dissection to those with inadequate nodal yield (< 18 nodes). We demonstrated that low nodal yield contributed to worse DFS (but not OS) both in univariate and multivariable analyses (p = 0.02 and p = 0.048, respectively, **Table S1**).

Survival for patients who had SND was at least equivalent to those who underwent MRND

Of the 122 patients, ten patients underwent bilateral neck dissection (8 base of tongue and 2 tonsil primaries). Fifty-two patients underwent MRND and 70 patients underwent SND. We compared DSS and OS between patients who underwent SND (n = 70) and those who underwent MRND (n = 52). To control for differences in patient and disease characteristics between the two groups we performed propensity score (PS) matching, choosing 52 patients from the SND group with similar characteristics to the 52 patients in the MRND group (**Table S3**). We determined that the MRND group had significantly

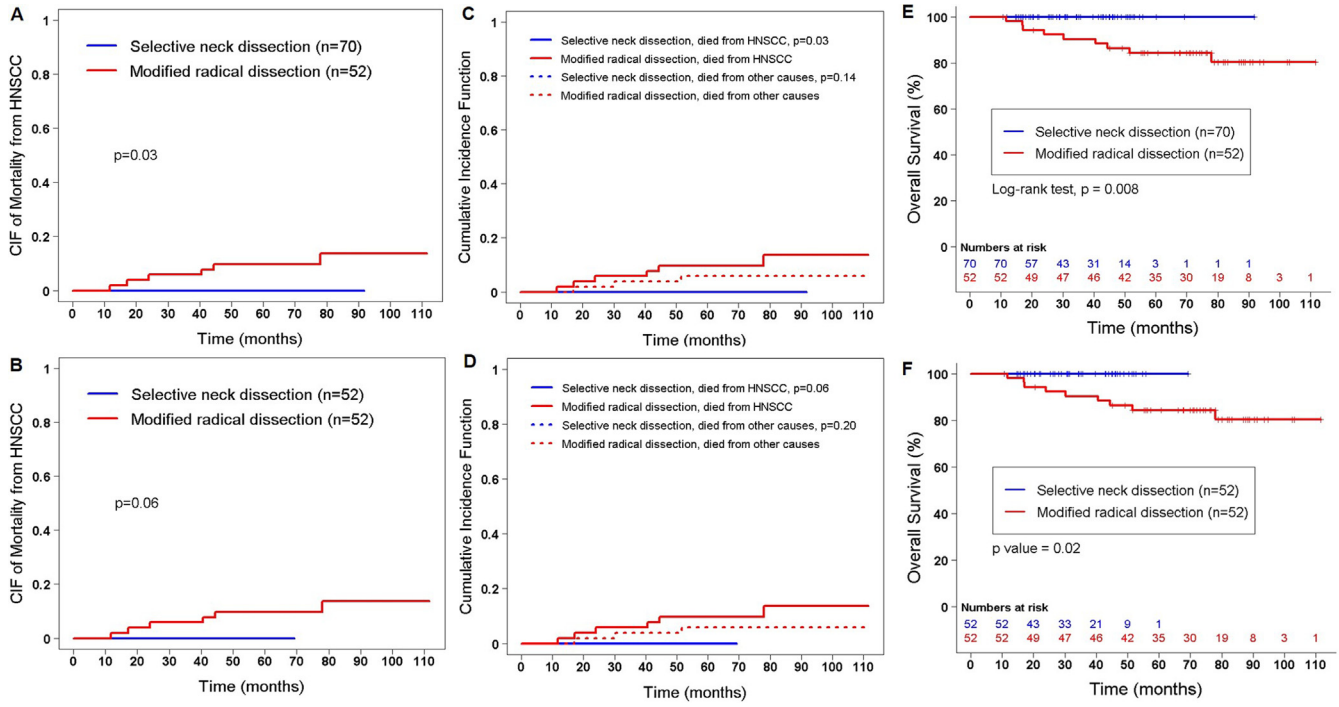

Fig. 4. MRND led to worse overall survival than SND. (A-B) Patients in the MRND group were significantly more likely to die of HNSCC (p = 0.03 before PS matching, p = 0.06 after PS matching. **(C-D)** There was no difference in likelihood of dying from causes other than HNSCC. **(E-F)** Patients in the MRND group had significantly worse overall survival than patients in the SND group (p = 0.008 before PS matching, p = 0.02 after PS matching).

increased risk of mortality from HNSCC compared to the SND group (*i.e.,* worse DSS, p = 0.03). With PS matching between the two groups the DSS comparison resulted in p = 0.06 (Fig. 4**A-B**). As deaths were rare (n = 9) in our study we also calculated the CIF for death from causes other than HNSCC (Fig. 4**C-D**), which was not different between MRND and SND groups. However, overall survival was significantly worse in the MRND group, both before and after PS matching (p = 0.008 and p = 0.02, respectively, Fig. 4**E-F**), indicating that the MRND group was more likely to die than the SND group, after controlling for all other factors.

Discussion

The purpose of this study was to determine disease outcomes in HPV-positive oropharyngeal carcinoma patients who underwent TORS, neck dissection and risk-adapted adjuvant therapy. We compared differences in disease outcome between different pathologic characteristics, namely those previously reported to impact survival including ENE, margin status, and nodal status. N2 status conferred significantly worse DSS and OS than N0/1 status on univariate analysis, but this statistical significance was not maintained in multivariable analysis. Patients with positive ENE and margins had equivalent survival to patients with negative ENE and margins, likely due to adjuvant chemoradiation.. Lastly, we demonstrated that patients who underwent MRND had significantly worse OS than patients who underwent SND, even after propensity score matching to normalize for differences in disease characteristics between the two groups. However, the small sample size of the study limited the impact of our findings.

Current standard of care for oropharyngeal carcinoma patients who undergo surgery involves risk-adapted adjuvant therapy. Patients with intermediate risk features, such as T3/T4 or N2 staging, perineural invasion or lymphovascular invasion, undergo postoperative radiation therapy [17]. Patients with high risk features, *i.e.,* ENE or positive margins, undergo chemoradiation [18,19]. However the clinical trials that established these risk categories were performed prior to the HPV era. In this study we showed that a third high risk factor, ≥5 metastatic nodes (*i.e.,* N2 staging), should be considered. Our results demonstrated that if patients are treated with adjuvant chemoradiation, presence of ENE and positive margins did not adversely impact survival. However, patients with ≥ 5 metastatic nodes had worse survival, despite adjuvant radiation or chemoradiation . Our finding was consistent with other case series, which also showed that patients with ≥ 5 metastatic nodes had substantially worse rates of disease recurrence, particularly distant metastasis [20,21]. In their study of 116 HPV-positive oropharyngeal carcinoma patients treated with either neck dissection and resection or brachytherapy of the primary tumor, Lee *et al.* showed that the single factor associated with worse three-year progression-free survival (PFS) is presence of five or more metastatic nodes [20]. Sinha *et al.* showed a four-fold (16% vs 4%) increase in distant metastasis with high-metastatic node number patients in their cohort of HPV-positive oropharyngeal carcinoma patients treated TORS and neck dissection [21]. In the initial study by Haughey *et al.* that formed the basis for the AJCC 8th edition staging system, patients with ≥ 5 pathologically positive nodes had a worse five-year overall survival (71% vs 84%) [22]. Our findings corroborate the study design of the recently completed Eastern Cooperative Oncology Group (ECOG) 3311 trial which considered ≥ 5 nodes to be high-risk. While our survival rate was high, our failures were in not being able to control distant metastasis, which accounted for deaths from disease in our cohort. This finding highlights the importance of systemic control. Our patients with N2 disease had impaired survival despite adjuvant chemoradiation, suggesting that a fourth modality such as immunotherapy may have an important role in HPV-positive oropharyngeal carcinoma treatment. The addition of immunotherapy after chemoradiation in patients with non-small cell lung cancer improved survival [23] and is an attractive strategy for consideration in our at-risk population.

Prior to the widespread adoption of TORS, concurrent chemoradiation (CCRT) was the standard of care for HPV-positive oropharyngeal SCC, with a three-year overall survival of 82.4% compared to just 57.1% for the HPV-negative group in the retrospective analysis of the Radiation Therapy Oncology Group (RTOG) 0129 trial by Ang *et al.* [2]. Currently there is a lack of level I evidence comparing upfront

surgery followed by risk-adapted adjuvant therapy to definitive CCRT in HPV-positive oropharyngeal carcinoma patients. However, several case series suggest that TORS for oropharyngeal SCC results in similar survival outcomes to definitive CCRT. A review of seventeen studies using TORS to treat oropharyngeal SCC demonstrates a two-year DFS between 79 and 89% and a two-year OS of 82–90% [14]. It should be noted that the RTOG 0129 trials, as well as many other CCRT trials, enrolled a higher proportion of late stage OPC patients than upfront surgery trials. The randomized, phase II ECOG 3311 trial assessed de-escalating treatment in HPV-positive intermediate-risk oropharyngeal carcinoma; patients underwent TORS followed by either low- or standard-dose radiation therapy. Results of this trial are still pending. Our cohort of 122 HPV-positive oropharyngeal SCC patients treated with TORS-based surgery and risk adapted adjuvant therapy with a median follow up of 4.3 years demonstrates a favorable OS rate of 91%.

Disease outcomes extracted from the National Cancer Data Base (NCDB) suggest that patients with early stage HPV-positive oropharyngeal SCC who undergo TORS have a survival advantage over those patients who receive definitive RT. Roden *et al.* identified a total of 3247 patients from the NCDB with T1 or T2 tonsil squamous cell carcinoma [4]. Although selection bias likely exists in these retrospective cohorts, they found that patients who underwent surgical tonsillectomy with elective neck dissection and/or adjuvant RT had significantly better survival than patients who had RT alone (81.1% vs 64.5% five-year OS).

Functional outcomes after TORS versus definitive CCRT is controversial. A recent systematic review of prospective and retrospective single-arm case series concludes that gastrostomy tube rates are between 0 and 9.5% at one year and 0% at two years for oropharyngeal SCC patients who undergo TORS followed by adjuvant therapy [14]. In contrast gastrostomy tube rates for definitive CCRT series range from 9 to 39% at one year. In our current study the rate of PEG dependence at one year was 0%. Two studies focused on quality of life (QOL) after TORS show that patients who undergo TORS alone have improved QOL at one year compared to patients who receive CCRT or TORS with risk-adapted adjuvant therapy [24,25]. A prospective study comparing stage III or IVA (AJCC 7th edition) oropharyngeal or supraglottic SCC patients who undergo TORS and adjuvant therapy to those who undergo definitive CCRT demonstrates that patients who undergo TORS and adjuvant therapy have significantly better MDADI scores than patients who undergo definitive CCRT at six and twelve months after treatment [26]. Even early stage oropharyngeal carcinoma patients treated with definitive chemoradiation have a significant functional deficit. In a retrospective pooled analysis from three single institutions of low-intermediate risk patients with oropharyngeal carcinoma treated with radiation and chemotherapy (induction or concurrent), up to 15% report poor swallowing function and persistently depressed MDADI scores on long-term follow up [27]. In contrast, a recently published prospective, randomized phase II trial (ORATOR) that compared survival and QOL in patients who were randomized to receive either TORS and risk adapted adjuvant therapy or CCRT found similar survival between the two groups [28]. Specifically, swallowing (MDADI), pain, trismus and shoulder impairment scores were better in the CCRT group, although the surgery group had less tinnitus/hearing loss, neutropenia and constipation. These data have led to a larger, randomized Phase III study evaluating QOL outcomes between these two approaches.

Our study is limited by the intrinsic bias of a single-institution retrospective analysis. Despite these limitations, we demonstrated 1) high disease-specific survival and excellent functional outcome with upfront TORS, neck dissection and risk-adapted therapy, 2) that after controlling for all other disease factors in our group of patients, survival outcomes for patients treated with SND are at least equivalent to MRND, and 3) that while TORS and adjuvant therapy result in equivalent survival for patients with extranodal extension and positive margins, high metastatic-node count is a poor prognostic factor and should be considered as such in future clinical trials.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2020.104770.

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