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Human Papillomavirus–Negative Oropharyngeal Cancer Survival Outcomes Based on Primary Treatment: National Cancer Database Analysis

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Abstract

Objective. To compare survival outcomes between primary surgery and primary radiation therapy (RT) in patients with human papillomavirus (HPV)–negative oropharyngeal squamous cell carcinoma (OPSCC).

Study Design. A retrospective observational cohort study.

Setting. National Cancer Database.

Methods. A National Cancer Database review was conducted of 2635 patients with HPV-negative OPSCC who underwent surgery or RT ± chemotherapy between 2010 and 2014. Univariate analysis was performed on all variables and entered into a multivariate model. The main outcome was overall survival (OS).

Results. A total of 2635 patients with HPV-negative OPSCC were organized into 4 groups based on cancer staging. In group 1 (T1-2 N0-1; n = 774), up-front surgery had significantly better 5-year OS (76.2%) than RT (56.8%; adjusted hazard ratio [aHR], 1.76; P = .009; 95% CI, 1.15-2.69) and chemoradiation therapy (CRT; 69.5%; aHR, 1.56; P = .019; 95% CI, 1.08-2.26). In group 2 (T3-4 N0-1; n = 327), no significant difference existed between surgery and CRT (5-year OS, 51.3% vs 52.4%; aHR, 0.96; P = .88; 95% CI, 0.54-1.69). In group 3a (T1-2 N2-3; n = 807), surgery with adjuvant treatment showed significantly better 5-year OS than CRT (78.6% vs 68.8%; aHR, 1.51; P = .027; 95% CI, 1.05-2.18). In group 3b (T3-4 N2-3; n = 737), surgery with adjuvant treatment was not statistically associated with better 5-year OS as compared with CRT (61.0% vs 43.7%; aHR, 1.53; P = .06; 95% CI, 0.98-2.39).

Conclusion. Primary surgery may provide improved survival outcomes in many cases of HPV-negative OPSCCs. These data should be used in weighing treatment options and may serve as a basis to better delineate treatment algorithms for HPV-negative disease.

Keywords

oropharyngeal cancer, HPV (negative), surgery, radiation, chemoradiation

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Over 20 years, oropharyngeal squamous cell carcinoma (OPSCC) has been divided into human papillomavirus (HPV) positive and HPV negative.[1] HPV-positive OPSCCs have superior survival when compared with HPV-negative counterparts.[2] During this period, the majority of new OPSCCs become HPV positive, and research efforts have focused on this group.[3] Data are scarce on survival outcomes for HPV-negative OPSCC.[4-6]

The eighth edition of the American Joint Committee on Cancer (AJCC) staging system separates OPSCC by HPV status.[2-7] National Comprehensive Cancer Network (NCCN) guidelines created separate algorithms based on HPV status.[8] Despite this division, OPSCC types have similar recommendations for up-front surgery and nonsurgical approaches.[8]

Historically, survival data did not subgroup OPSCC by HPV status.[4,5,8] Based on several retrospective series, with

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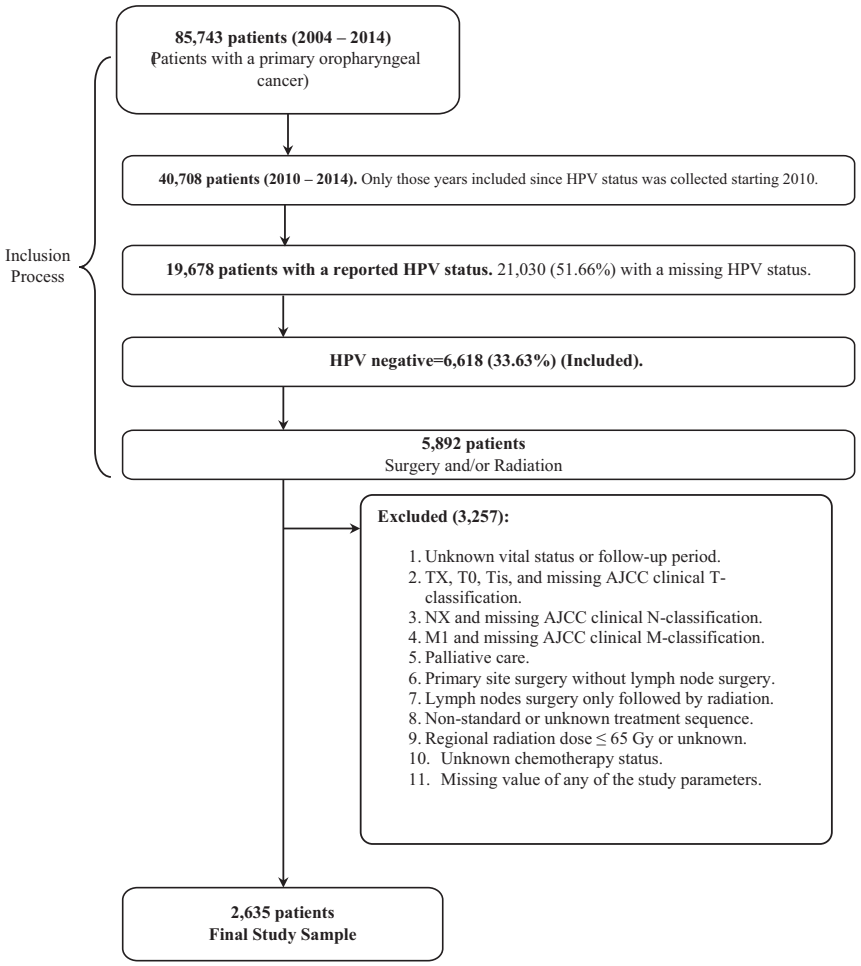

Figure 1. Flowchart: systematic process used in the current study for patients' inclusion and exclusion. Study population included patients with squamous cell carcinoma (code 807 and primary site codes C019, C024, C051, C052, C090, C091, C098, C099, C100, C101, C102, C103, C104, C108, and C109). AJCC, American Joint Committee on Cancer; HPV, human papillomavirus.

the hope of diminishing toxicity through organ preservation,[1,2] it became a common notion that OPSCC is best treated with chemoradiation therapy (CRT). However, these data were likely skewed by the inclusion of HPV-positive disease. Thus, the question remains: which treatment paradigm provides the best survival outcome for HPV-negative OPSCC based on clinical staging?

The aim was to determine the overall survival (OS) differences in HPV-negative OPSCC by treatment modality. The National Cancer Database (NCDB) was employed to obtain a hospital-based cohort.

Methods

Data Source and Inclusion/Exclusion Criteria

The NCDB is a hospital-based registry collecting data from >1500 Commission on Cancer–approved hospitals in the United States. It captures 70% of newly diagnosed cancers. The 2015 head and neck NCDB participant user file was accessed; it contains patient demographics, cancer characteristics, treatment modalities, and OS. This study is exempt from Institutional Review Board approval (University of Florida).

From 2004 to 2014, 85,743 patients with OPSCC were registered in the NCDB. Oropharyngeal primary site codes were selected: C019, C024, C051, C052, C090, C091, C098, C099, C100, C101, C102, C103, C104, C108, C109. Since 2010, 19,678 patients with known HPV status were reported. The inclusion/exclusion criteria are described in **Figure 1**. The first-echelon inclusion criterion was OPSCC with HPV-negative squamous cell carcinoma histology (code 807; *International Classification of Disease for Oncology, Third Edition*); the remaining cases were excluded[9] and 6618 patients remained. Next, patients with missing/unknown clinical TNM/AJCC staging, vital status, or follow-up were excluded. M_1 classification or patients under palliative care were removed.

The second level of inclusion criteria defined curative-intent treatment based on the 2019 NCCN guidelines.[8] This included patients who underwent definitive primary surgery or definitive primary radiation therapy (RT) ± chemotherapy. Definitive primary surgery was defined as wide local excision

of the primary tumor with neck dissection. All other forms of incomplete resection were excluded. These included codes 10 to 15, 90, and 99, which represent unknown surgical status, partial tumor removal, excisional biopsy, or a combination of non–curative intent modalities. None of these categories were associated with neck dissection and likely represented various forms of large biopsies (eg, tonsillectomy, base of tongue mucosectomy, excisional lesion biopsy). These incomplete resections did not include curative-intent surgery with positive margins. There was a separate column for margin status. Those who underwent primary tumor resection without neck dissection or a neck dissection without primary tumor resection before RT were also excluded. Patients with curative-intent RT ± chemotherapy who had unknown RT dose, dose <66 Gy, unknown or nonstandard RT delivery method, unknown or nonstandard sequence of surgery-RT modalities, or unknown chemotherapy status were excluded. The sequence of treatment modalities was listed as surgery, RT, CRT, or surgery followed by RT or CRT. A total of 2635 patient records remained for analysis.

Patient Groups

The NCCN guidelines stratify cases by T and N classifications instead of overall staging.[8] This allows multidisciplinary groups to provide case-specific treatment options instead of generalizing by early or late stage. The goal of this study was to validate these algorithms and determine if recommendations correspond with optimal survival outcomes. Thus, the study population was grouped by the same groups that the NCCN guidelines use.

The study population was divided into 3 groups based on NCCN treatment decision categories: group 1, T1-2 N0-1; group 2, T3-4 N0-1; and group 3, T1-4 N2-3.[8] Because T classification is often the first decision-making branch in the NCCN algorithms and plays a major role in deciding treatment approach, the third group was split into 2 subcategories: group 3a, T1-2 N2-3; group 3b, T3-4 N2-3. The reason for this split is that the treatment options for T1-T2 and T3-T4 are very different (ie, transoral surgery vs unilateral RT fields or open surgery vs bilateral RT fields).

Treatment Packages

Based on highest level of evidence used by the NCCN (level 2a), appropriate treatment packages were included, and all inappropriate options, as referenced by the NCCN (level 2b and 3), were excluded.[8] For example, single-modality treatment of surgery or RT from the cT3-4 groups was excluded, and single-modality RT for group 3a (cT1-2 N2-3) was excluded. Surgery only was included for cT1-2 N2-3 because in many cases, the final staging was pT1-2 N0-1, and adjuvant RT was not necessary.

Data Points

Demographics, tumor characteristics, and treatment details were included. Age was dichotomized at the mean of 65 years. Race was classified as White/non-White. Insurance status was classified as follows: no insurance and Medicaid or Medicare, private insurance, and governmental insurance. Comorbidities were scored by Charlson-Deyo score: 0-1 or ≥2. Oropharyngeal subsites were classified as base of tongue, soft palate, tonsil, and oropharyngeal walls. Lymphovascular invasion data were collected where reported. Perineural invasion is not included in the NSDB and could not be reported. Other factors known to influence survival (eg, smoking status) were also not available. Clinical AJCC staging, seventh edition, was used instead of pathologic staging to allow direct comparison between surgical and nonsurgical groups. AJCC staging, eighth edition, could not be used, as extranodal extension is not coded in the NCDB. Staging was based on clinical staging, as pathologic staging is not available in patients treated with RT. This allowed for comparisons with a common baseline. Because treatment decisions are founded on clinical staging, this was used to analyze outcomes.

Statistical Analysis

Survival analysis was performed separately for each treatment group. OS was defined as time between diagnosis and death or end of follow-up. Median survival was estimated with the Kaplan-Meier product limit method, and significant differences between survival times were determined with the log-rank test. Independent prognostic factors for OS, hazard ratio (HR), and 95% CI were calculated with Cox proportional hazard models. A multivariate Cox HR model controlled for age, sex, race, insurance status, comorbidity status, and cancer site. Patients were analyzed in an intent-to-treat manner and did not cross over between treatment groups. HR >1 corresponded to worse OS (increased likelihood of death). All tests were 2-sided with $P < .05$ considered significant. Patient, clinical, and treatment variables were selected a priori. Statistical analyses were performed with SAS version 9.3 (SAS Institute Inc).

Results

A total of 2635 cases of HPV-negative OPSCC were included (1983 men, 75.3%; 652 women, 24.7%): 774 in group 1 (T1-2 N0-1), 327 in group 2 (T3-4 N0-1), 807 in group 3a (T1-2 N2-3), and 727 in group 3b (T3-4 N2-3). Baseline characteristics are shown in **Table 1**.

The mean ± SD age was 59.7 ± 9.8 years; 2260 were White (85.8%) and 375 were non-White (14.2%). The median follow-up time was 34.8 months (interquartile range, 15.4-53.2 months); >90% of patients were insured; and >80% were comorbidity free (**Table 1**). Tonsil (n = 1163, 44.1%) and base of tongue (n = 989, 37.5%) were the most common subsites; soft palate was the least common (n = 175, 6.6%). Lymphovascular invasion was reported in 35.4% of patients (137 positive, 14.7%; 796 negative, 85.3%). Up-front surgery pathologically upstaged 66 cases in clinical T classifications (8.8%) and 63 in N classifications (8.4%).

Significant variables from the univariate analysis were inserted into the multivariate Cox regression model. All variables showed significance ($P < .05$) in the multivariate model.

Table 1. Study Population of Patients With Human Papilloma Virus–Negative Oropharyngeal Squamous Cell Carcinoma: National Cancer Database, 2010-2014.[a]

		AJCC clinical stage				
	Study population (N = 2635)	Group 1: T1-2 N0-1 (n = 774)	Group 2: T3-4 N0-1 (n = 327)	Group 3a: T1-2 N2-3 (n = 807)	Group 3b: T3-4 N2-3 (n = 727)	*P* value[b]
Age, y						
<65	1852 (70.28)	516 (66.67)	217 (66.36)	583 (72.24)	536 (73.73)	
≥65	783 (29.72)	258 (33.33)	110 (33.64)	224 (27.76)	191 (26.27)	.005
Sex						
Male	1983 (75.26)	509 (65.76)	257 (78.59)	650 (80.55)	567 (77.99)	
Female	652 (24.74)	265 (34.24)	70 (21.41)	157 (19.45)	160 (22.01)	<.001
Race						
White	2260 (85.77)	687 (88.76)	278 (85.02)	717 (88.85)	578 (79.5)	
Non-White	375 (14.23)	87 (11.24)	49 (14.98)	90 (11.15)	149 (20.5)	<.001
Type of insurance						
No insurance, Medicaid	527 (20)	104 (13.44)	64 (19.57)	136 (16.85)	223 (30.67)	
Private, Medicare, other governmental	2108 (80)	670 (86.56)	263 (80.43)	671 (83.15)	504 (69.33)	<.001
Charlson-Deyo score						
0-1	2517 (95.52)	730 (94.32)	306 (93.58)	783 (97.03)	698 (96.01)	
≥2	118 (4.48)	44 (5.68)	21 (6.42)	24 (2.97)	29 (3.99)	<.001
Site of cancer						
Base of tongue	989 (37.53)	265 (34.24)	112 (34.25)	299 (34.25)	313 (43.05)	
Soft palate	175 (6.64)	94 (12.14)	24 (7.34)	25 (7.34)	32 (4.4)	
Tonsil	1163 (44.14)	340 (43.93)	125 (38.23)	416 (38.23)	282 (38.79)	
Oropharyngeal walls	308 (11.69)	75 (9.69)	66 (20.18)	67 (20.18)	100 (13.76)	<.001
Treatment type						
Surgery only	302 (11.46)	263 (33.98)	0 (0)	39 (4.83)	0 (0)	
RT only	128 (4.86)	128 (16.54)	0 (0)	0 (0)	0 (0)	
RT + CT only	1751 (66.45)	226 (29.2)	292 (89.3)	562 (69.64)	671 (92.3)	
Surgery + adjuvant RT/CT	454 (17.23)	157 (20.28)	35 (10.7)	206 (25.53)	56 (7.7)	<.001
T upstaged following surgery[c]						
Not upstaged	682 (91.18)	375 (89.71)		225 (92.98)		
Pathologically upstaged	66 (8.82)	43 (10.29)		17 (7.02)		
N upstaged following surgery[c]						
Not upstaged	685 (91.58)	368 (88.04)				
Pathologically upstaged	63 (8.42)	50 (11.96)				
Lymphovascular invasion						
Negative	796 (85.32)	365 (92.88)	88 (83.81)	213 (78.31)	130 (79.75)	
Positive	137 (14.68)	28 (7.12)	17 (16.19)	59 (21.69)	33 (20.25)	<.001

Abbreviations: AJCC, American Joint Committee on Cancer; CT, chemotherapy; RT, radiotherapy.

Note: The treatment is based on the level of evidence (level 2a) used by the National Comprehensive Cancer Network. Appropriate treatment packages were included, and the inappropriate options, as referenced by the network (level 2b and 3), were excluded.

[a]Values are presented as No. (%). Percentage values may not add up to 100% due to rounding.

[b]Chi-square test.

[c]Blank cells indicate *not applicable* due to the data use agreement stipulating that a sample size <10 should not be reported.

[d]The treatment is based on the level of evidence (level 2a) used by the National Comprehensive Cancer Network. Appropriate treatment packages were included, and the inappropriate options, as referenced by the network (level 2b and 3), were excluded.

Patients in group 1 (T1-2 N0-1), who received up-front surgery without adjuvant treatment as a reference, had significantly better 5-year OS (76.2%) than either RT (56.8%; adjusted HR [aHR], 1.76; 95% CI, 1.15-2.69; $P = .009$) or CRT (69.5%; aHR, 1.56; 95% CI, 1.08-2.26; $P = .019$). Adding adjuvant treatment after surgery did not add any significant survival advantage when compared with surgery alone (77.4%; aHR, 1.16; 95% CI, 0.74-1.84, $P = .52$). Treatment outcomes are in **Table 2** and Supplemental Table S1 (available online). Kaplan-Meier analysis of survival by treatment modality for the 4 groups is in **Figure 2**.

In group 2 (T3-4 N0-1), 2 appropriate NCCN-recommended treatment regimens were used: surgery followed by adjuvant treatment versus primary CRT.[8] There was no

Table 2. Overall Survival in Patients With Human Papillomavirus–Negative Oropharyngeal Squamous Cell Carcinoma Based on Treatment.

AJCC group: treatment type	5-y overall survival, %	aHR[a]	95% CI	*P* value
T1-2 N0-1				
Surgery only	76.15	Reference		
RT only	56.79	1.76	1.15-2.69	.009
RT + CT only	69.53	1.56	1.08-2.26	.019
Surgery + adjuvant RT/CT	77.39	1.16	0.74-1.84	.52
T3-4 N0-1				
RT + CT only	52.35	0.96	0.54-1.69	.88
Surgery + adjuvant RT/CT	51.25	Reference		
T1-2 N2-3				
Surgery only	72.10	1.71	0.85-3.46	.13
RT + CT only	68.78	1.51	1.05-2.18	.027
Surgery + adjuvant RT/CT	78.59	Reference		
T3-4 N2-3				
RT + CT only	43.72	1.53	0.98-2.39	.06
Surgery + adjuvant RT/CT	61.02	Reference		

Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CT, chemotherapy; RT, radiotherapy.
[a]Multivariate Cox hazard ratio model controlling for age, sex, race, insurance status, comorbidities status, and site of cancer.

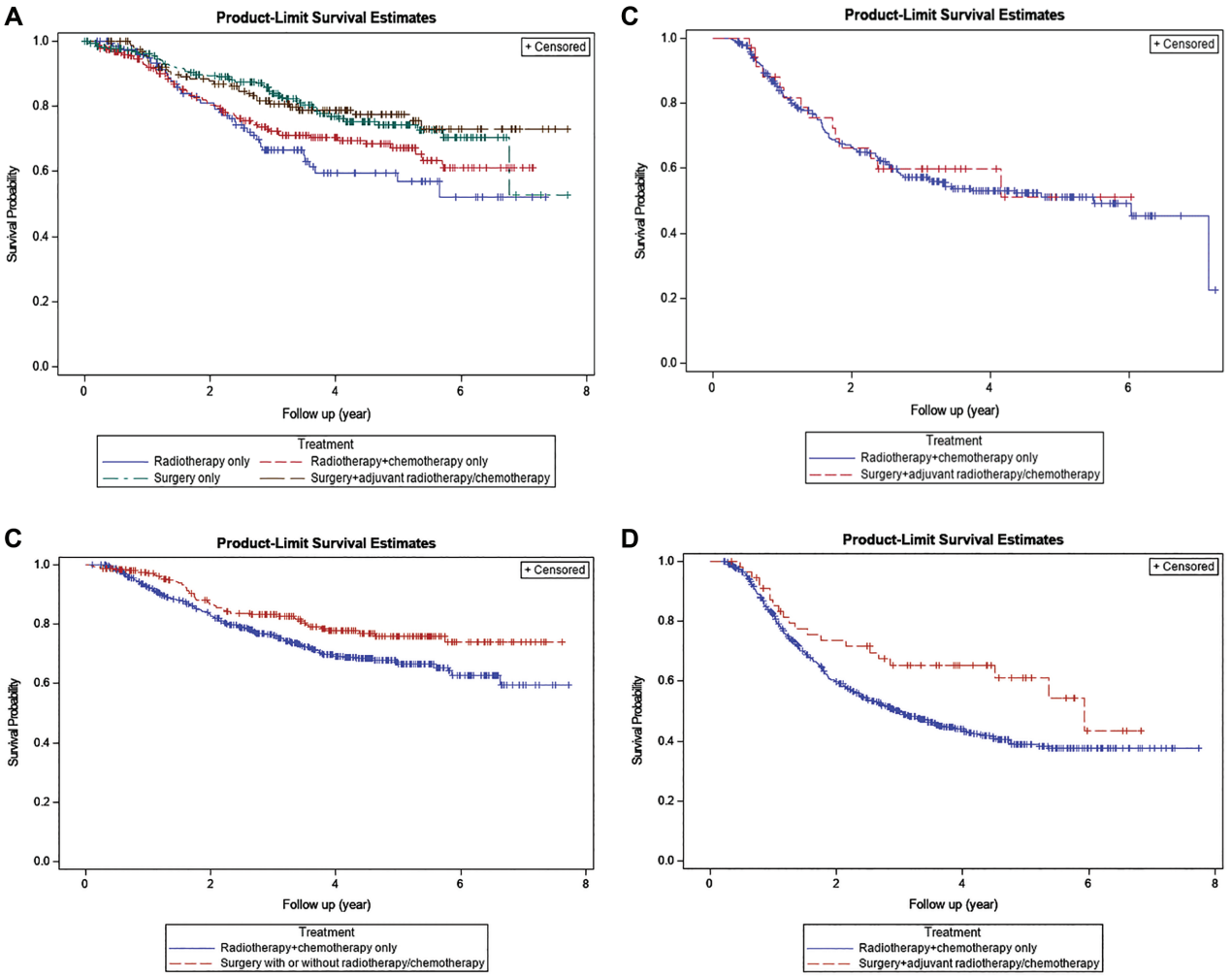

Figure 2. Kaplan-Meier analysis of survival by treatment modality: (A-D) group 1, T1-2 N0-1; group 2, T3-4 N0-1; group 3a, T1-2 N2-3; group 3b, T3-4 N2-3.

Table 3. Review of Literature.

First author	Year	No. of patients		Stage	Modalities	Outcomes		
		Total	HPV–			Survival	%	*P* value
Hobbs[14]	2017	357	39	All	Surgery vs CRT	DSS	56 vs 19	.04
						OS	50 vs 19	.058
						RFS	—	.22
Kelly[10,a]	2017	1044	1044	T1-2N1-2b	Surgery vs CRT	OS	HR, 1.01	.93
Mahmoud[11,a]	2017	1873	515	All	TORS vs nonsurgical	3-y OS	84 vs 66	.01
Seikaly[13]	2015	279	84	III and IV	Surgery with adjuvant vs CRT	5-y DSS (smokers)	60.3 vs 27.4	<.001
						5-y DSS (nonsmokers)	100 vs 80	.009
						OS (smokers)	43.1 vs 20.8	.003
						OS (nonsmokers)	85.7 vs 60	.24
Zenga[17]	2015	131	34	T4	Surgery vs nonsurgical	OS, DSS, DFS	Surgery better with significant DFS	.1, .15, .049

Abbreviations: CRT, chemoradiation; DFS, disease-free survival; DSS, disease-specific survival; HPV, human papillomavirus; HR, hazard ratio; OS, overall survival; RFS, recurrent-free survival; TORS, transoral robotic surgery.
[a]National Cancer Database.

significant difference in 5-year OS between them (51.3% vs 52.4%; aHR, 0.96; 95% CI, 0.54-1.69; $P = .88$; **Table 2** and Supplemental Table S2, available online). In group 3a (T1-2 N2-3), patients who received surgery with adjuvant treatment had significantly better 5-year OS than primary CRT (78.6% vs 68.8%; aHR, 1.51; 95% CI, 1.05-2.18; $P = .027$). Surgery alone had worse 5-year OS than surgery with adjuvant treatment (72.1% vs 78.6%); this difference was not significant (aHR, 1.71; 95% CI, 0.85-3.46; $P = .13$; **Table 2** and Supplemental Table S3).

In group 3b (T3-4 N2-3), surgery with adjuvant treatment had substantially better 5-year OS than primary CRT (61.0% vs 43.7%), but this was not statistically significant (aHR, 1.53; 95% CI, 0.98-2.39; $P = .06$; **Table 2** and Supplemental Table S4, available online). Population at risk of mortality as classified by stage and type of therapy was calculated and is shown in Supplemental Table S5. A parallel analysis was performed through pathologic T/N classifications, and the results are shown in Supplemental Table S6.

Discussion

T1-T2 HPV-negative OPSCCs appear to have improved OS with primary surgical approaches. This is the first study to use a large population database to demonstrate this. While this was not the first study to use a national hospital-based registry to study HPV-negative OPSCC, it is the first to stratify patients by best practice treatment modalities per national guidelines.[10,11]

Group 1 (T1-2 N0-1), surgery alone had significantly better 5-year OS than RT or CRT (7% to 19% improvement). Adding adjuvant treatment to surgery did not have any significant benefit, which parallels the results of Yuan et al.[12] They analyzed 114 patients treated with primary surgery for HPV-negative OPSCC. Disease-specific survival was affected by adjuvant RT in stages III and IV but did not show any benefit in stages I and II.[12] It is thought that many of these patients will have borderline or minimal indications for adjuvant treatment and will not receive additional benefit from postoperative RT. For example, in some patients, N1 status will provide a debatable indication for adjuvant treatment.[10,12-14] A comparative literature review is shown in **Table 3**.

For group 3a (T1-2 N2-3), surgery followed by adjuvant treatment showed significantly better 5-year OS than primary CRT (10% improvement). Kelly et al compared up-front surgery versus nonsurgical modalities in HPV-negative OPSCC within the NCDB, but they did not include N0, N2c, and N3 in their study.[10] Their data were limited to 2010 to 2012 and followed the RTOG 1221 (NCT01953952) design, which attempted to randomize patients with cT1-2 N1-2b HPV-negative OPSCC to transoral robotic surgery or CRT but closed due to a lack of accrual. The total population of T1-2 N1-2b was 1044 patients; there was no significant OS difference between patients with up-front surgery 460 (44.1%) and patients with CRT 584 (55.9%). The current study stratified patients by NCCN algorithms to compare results with national guidelines. In groups 1 and 3b together (T1-2 N0-1/T1-2 N2-3), there were 1581 patients: 665 (42%) had surgery, 128 (8%) received RT, and 788 (50%) underwent CRT. Up-front surgery in both groups had significantly better survival than nonsurgical options ($P < .05$). These results differ from Kelly et al and may be explained by the groups having different TNM and that all forms of incomplete surgery were excluded[10] (**Table 3**). Additionally, there may have been some inherent biases, such as health status and tumor site (eg, tonsil cancers are much ''easier'' to excise than base of tongue). To best account for these factors, the Cox regression analysis included them as controls.

In group 3a (T1-2 N2-3), patients treated with surgery only had statistically similar survival to those who were treated with adjuvant therapy. This likely demonstrates the accurate

staging value of surgery. With final pathology results, some cases were downstaged, and patients did not meet indications for adjuvant treatment. Conversely, some cases were upstaged, and patients required adjuvant treatment to maintain a similar survival to their counterparts treated with surgery only. This is similar to previous literature examining how final pathology influences adjuvant treatment and survival.[10-14]

Apart from Kelly et al, our findings are consistent with most literature. Comparison is difficult because each study followed a different stratification approach. For example, some studies used TNM (T1-2 N1-2b; Kelly et al), and other studies (Seikaly et al) used overall staging[10,13] (**Table 3**).

Like Kelly et al, Mahmoud et al used the NCDB. They analyzed 515 HPV-negative cases and found that patients undergoing primary transoral robotic surgery had significantly better 3-year OS than those treated via nonsurgical modalities (84% vs 66%, $P = .01$). But they did not stratify the HPV-negative population according to staging; rather, the cohort included patients with HPV-negative and HPV-positive OPSCC.[11] Seikaly et al studied 84 patients who had HPV-negative OPSCC with stage III/IV disease; in univariate analysis, primary surgery with adjuvant treatment yielded significantly better 5-year disease-specific survival and OS (72.0% and 54.8%, $P < .001$) than primary CRT (37.1% and 27.6%, $P < .001$). Multivariate analysis showed a significant survival advantage with surgical treatment.[13] Hobbs et al showed that surgery with adjuvant treatment had improved disease-specific survival (HR, 0.43; $P = .015$) and OS (HR, 0.49; $P = .26$) than CRT in 26 patients[14] (**Table 3**). These data are consistent with our study.

For group 2 (T3-4 N0-1), patients with up-front surgery and adjuvant treatment did not have survival benefit over those who received primary CRT. The lack of statistical difference is likely due to the control rates for N0 and N1 being similar for surgery and CRT.[15]

In group 3b (T3-4 N2-3), primary surgery with adjuvant treatment had 17.3% better 5-year OS than CRT and neared significance ($P = .06$). Surgical approaches for T3-4 disease often carry a higher risk of positive margins and complications, which also affect survival.[16] The advanced neck disease could be the reason for a survival advantage with surgery in T3-4 N2-3. For most head and neck cancer sites, advanced neck disease is best cured with surgery plus adjuvant treatment.[15] This was similar to 34 patients with T4 HPV-negative OPSCC in the study by Zenga et al. OS and disease-specific survival were higher in the surgical group without statistical significance ($\chi^2 = 2.649$, $df = 1$, for log-rank $P = .10$ and $\chi^2 = 2.077$, $df = 1$, for log-rank $P = .15$, respectively), but disease-free survival was significantly higher in patients treated with primary surgery ($\chi^2 = 3.869$, $df = 1$, for log-rank $P = .049$; **Table 3**).[17]

It is prudent to remember that surgery functions as a tool of diagnosis/prognosis. In this study, surgery upstaged >10% of T/ N clinical classifications in group 1 (T1-2 N0-1). The result was more intensified adjuvant treatment. If a nonsurgical modality were used, it would likely have been RT only, which may not have provided as high a cure rate.[18] It was determined that patients in groups 2 to 3b faired worse when pathologic staging was used to analyze OS. It is likley that patients who had worse pathology received adjuvant therapy. However, the adjuvant therapy in these cases did not seem to make much of a difference. The only patients who did better in this scenario were those with early-stage OPSCC (group 1). Thus, when a treatment option for more advanced disease is being chosen, these factors must be considered.

Although many patients with HPV-negative OPSCCs can have improved survival with primary surgery, this must be taken into context with functional and quality-of-life outcomes. While a small tonsil primary may do very well functionally with surgery, a deep base of tongue primary may require a total glossectomy and may do very poorly with surgery. The results of this study suggest that surgery should be a part of the discussion in treatment recommendations, but recommendations should strive to balance survival with functional outcomes and quality of life. Each case is unique, and a multidisciplinary discussion is needed to tailor treatment for each patient.

Limitations

The NCDB does not allow control for all confounding factors. Some variables known to influence survival are not in the database, such as perineural invasion, extranodal extension, and smoking status. These must be taken into consideration when interpreting results as they may influence treatment decisions. This is especially true for extranodal extension, which has such a strong influence on survival that it was added into the eighth edition of the AJCC staging system. OS is a crude measure of treatment efficacy; it is determined by death from any cause, and there are many competing causes of death in cases of OPSCC. Although the multivariate analysis controlled for comorbid status (Charlson-Deyo score), it is possible that healthier patients were selected for primary surgery. This could account for the large difference in OS for group 3b. In that group, few patients had primary surgery versus CRT, and the unaccounted-for variable could be hiding in other health conditions. The other possibility is that functional outcomes were not taken into account and surgery was not offered to patients with larger tumors.

Although the NCDB is the largest cancer database in the United States, the accuracy of registration can be limited. In gathering records, the number of patients dropped from 6618 to 2635; almost two-thirds of the population were omitted to provide complete data that met study criteria. This may have created selection bias; however, without application of study criteria, data would be too heterogeneous to have meaning. The study included the most complete and accurate data possible.

We excluded modalities with less evidence-based application by the NCCN (eg, induction chemotherapy). Although Sher et al showed that induction chemotherapy had significant benefit for highly advanced HPV-negative OPSCC (T4N3), these results have not been reproduced.[19] Also, we could not stratify patients by type of surgery (transoral vs open) because this variable was not accurately registered.

To promote individualized patient-centered care, the patient's preferences should be considered. The patient

should certainly be educated regarding survival differences and the pros and cons of each treatment pathway. The patient has the right to choose options that show lower survival rates to avoid the highly morbid options. Major long-term RT complications, such as osteoradionecrosis and dysphagia, need to be considered.[20,21]

A randomized clinical trial would be needed to determine the optimal treatment modality for HPV-negative OPSCC. Unfortunately, it is difficult to enroll patients in trials with surgical and nonsurgical arms as shown by RTOG 1221. In the absence of randomized prospective data, national database analyses can be the next available level of evidence.

Conclusion

Primary surgery may provide improved survival outcomes for many HPV-negative OPSCCs. These data may be used in weighing treatment options with patients and may help better delineate treatment algorithms for HPV-negative disease.

Author Contributions

Mohamed Shama, conception and design of study, analysis and interpretation of data, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work; **Zaid Al-Qurayshi,** conception and design of study, analysis and interpretation of data, final approval of manuscript, agreement to be accountable for all aspects of the work; **Mohammad Dahl**, conception and design of study, analysis and interpretation of data, agreement to be accountable for all aspects of the work; **Robert J. Amdur**, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work; **James Bates**, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work; **William Mendenhall**, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work; **Kathryn Hitchcock**, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work; **Bianca M. Festa**, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work; **Tamer Ghanem**, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work; **Peter T. Dziegielewski**, conception and design of study, analysis and interpretation of data, drafting and critically revising work, final approval of manuscript, agreement to be accountable for all aspects of the work.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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