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Evaluating Adjuvant Therapy With Chemoradiation vs Radiation Alone for Patients With HPV-Negative N2a Head and Neck Cancer

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IMPORTANCE The American Joint Committee on Cancer staging system (*Cancer Staging Manual, 8th Edition*) for head and neck squamous cell carcinoma (HNSCC) now categorizes human papillomavirus (HPV)–negative HNSCC in a single positive lymph node smaller than 3 cm with pathologic extranodal extension (ENE) as N2a. The standard of care for pathologic ENE is adjuvant chemoradiation therapy (CRT). Whether adding chemotherapy concurrent with adjuvant radiation therapy improves survival in this clinical scenario is unknown.

OBJECTIVE To assess whether adjuvant CRT relative to radiation therapy alone is associated with improved survival among patients with pN2a HPV-negative HNSCC with ENE.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included 504 patients with pN2a HPV-negative HNSCC with ENE who had undergone margin-negative surgery and adjuvant therapy. The patients were identified from the National Cancer Database from January 1, 2004, to December 31, 2015. Statistical analyses were conducted from September 1, 2019, to April 16, 2020.

MAIN OUTCOMES AND MEASURES The primary end point was overall survival. The association of adjuvant CRT with overall survival was analyzed using univariate and multivariate Cox proportional hazards regression analyses. Planned subset analyses were conducted in patients younger than 70 years with no comorbidities (the subset most likely to be eligible for a clinical trial of cisplatin-based chemoradiation) and in patients with pT3/T4 disease classification.

RESULTS Of 504 patients (mean [SD] age, 60.5 [12.7] years; 319 [63.3%] men; 434 [86.1%] White) with pN2a HPV-negative HNSCC with ENE who had undergone margin-negative surgery and adjuvant therapy, 298 patients (59.1%) received adjuvant CRT. For the overall cohort of patients with pN2a ENE, adjuvant CRT was not associated with improved overall survival relative to adjuvant radiation therapy alone in a multivariate analysis (adjusted hazard ratio, 0.98; 95% CI, 0.74-1.30). Adjuvant CRT was still not associated with improved overall survival in a subset analysis of 304 patients younger than 70 years with no comorbidities (adjusted hazard ratio, 0.98; 95% CI, 0.66-1.45) nor in a subset of 220 patients with pT3/T4 disease classification (adjusted hazard ratio, 1.03; 95% CI, 0.70-1.54).

CONCLUSIONS AND RELEVANCE This study found that for patients with pN2a HPV-negative HNSCC with ENE who underwent margin-negative surgery and adjuvant therapy, adding chemotherapy concurrent with adjuvant radiation therapy was not associated with improved overall survival. Additional research is necessary to identify the optimal treatment paradigm for this clinical scenario.

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Supplemental content

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Head and neck squamous cell carcinoma (HNSCC) represents a malignant neoplasm that has seen relatively modest improvements in survival during the last few decades, especially for human papillomavirus (HPV)–negative and smoking-related cancers. Patients with HNSCC commonly receive this diagnosis at late stages, thus requiring multimodality therapy as the standard of care.[1] This multimodality therapy often includes surgery followed by adjuvant radiation therapy (RT) or adjuvant chemoradiation therapy (CRT).[2] Standard of care per National Comprehensive Cancer Network guidelines for pathologic extranodal extension (ENE)–positive HNSCC, based on 2 landmark randomized clinical trials (RCTs),[3,4] is adjuvant CRT.[2] Although adding chemotherapy concurrent with adjuvant RT improved disease-free survival (DFS) in Radiation Therapy Oncology Group (RTOG) 9501 and overall survival (OS) in European Organization for Research and Treatment of Cancer Trial (EORTC) 22931, it also significantly increased short- and long-term morbidity and contributed to decreased functional outcomes.[3-5]

The *American Joint Committee on Cancer Staging Manual, 8th Edition* (*AJCC8*), introduced pathologic ENE into the staging criteria for HPV-negative HNSCC.[6,7] This led to the creation of 2 new nodal classifications for patients with HPV-negative HNSCC: pN2a for those with a single positive lymph node (LN) smaller than 3 cm with pathologic ENE, and pN3b for those with pathologic ENE in a single LN larger than 3 cm or in multiple LNs. Human papillomavirus–negative, ENE-positive tumors with a single LN metastasis smaller than 3 cm (pN2a) represent a subset of ENE-positive tumors that have not been previously examined. Whether adding chemotherapy improves patient survival in this clinical situation is unknown.

Therefore, the aim of this study was to evaluate whether adding chemotherapy concurrent with adjuvant RT is associated with improved OS relative to adjuvant RT for patients with pN2a HPV-negative HNSCC with ENE.

Key Points

Question Is the addition of chemotherapy to adjuvant radiation therapy associated with improved survival among patients with human papillomavirus–negative head and neck squamous cell carcinoma with extranodal extension in a single lymph node smaller than 3 cm (*American Joint Committee on Cancer Staging Manual, 8th Edition*, category pN2a)?

Findings In this cohort study of 504 patients from the National Cancer Database with pN2a human papillomavirus–negative head and neck squamous cell carcinoma who underwent margin-negative resection, adjuvant chemoradiation therapy was not associated with improved overall survival relative to adjuvant radiation therapy alone.

Meaning Adding chemotherapy to adjuvant radiation therapy was not associated with improved survival in this study, suggesting the need for additional research to identify optimal treatment paradigms for these patients.

Methods

Database

Deidentified patient data from the National Cancer Database (NCDB) were used for this study. The NCDB is a hospital-based cancer registry that is a joint program of the American College of Surgeons Commission on Cancer and the American Cancer Society. The NCDB annually collects data from more than 1500 Commission on Cancer–accredited hospitals in the US, capturing more than 70% of newly diagnosed cancer cases annually in the US.[8] Although the NCDB is not a population-based database, such as the Surveillance, Epidemiology, and End Results database, it reflects characteristics of population-based data in terms of demographic characteristics, staging, and treatment for patients with HNSCC.[9] This study was deemed exempt from review by the institutional review board at the Medical University of South Carolina. No one received compensation or was offered any incentive for participating in this study.

Study Cohort

Patients with pathologically confirmed HPV-negative HNSCC with a single LN metastasis smaller than 3 cm showing ENE (ie, pN2A per AJCC8) undergoing margin-negative primary resection and adjuvant therapy from 2004 to 2015 were identified in the NCDB. The HNSCC diagnosis was based on the *International Classification of Disease for Oncology, 3rd Edition*, classification of oral cavity, oropharynx, hypopharynx, and larynx subsites and squamous cell carcinoma histology (eTable 1 in the Supplement).[10] All HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) tumors were excluded to avoid potential confounding by ENE status and because the effect of adjuvant CRT on oncologic outcomes for patients with ENE in this population is an area of clinical uncertainty and ongoing research.[11,12] Because HPV status was not incorporated into the NCDB until 2010, we excluded all OPSCC cases prior to 2010 and HPV-positive or HPV-unknown OPSCC cases from 2010 to 2015. Primary surgical resection was defined by NCDB codes 20 to 80.[13] We excluded patients with margin-positive or unknown margin status to remove this potential confounding variable. Only patients with pathologic ENE were included in the study. These cases were identified in the NCDB using Collaborative Stage Site-Specific factor 2 for cases diagnosed prior to 2010 (coded as present or absent) and factor 9 from 2010 onward (coded as microscopic [≤2 mm], macroscopic [>2 mm], or without further specification).[14] Owing to the amount of missing data regarding the extent of ENE, it was impossible to further subdivide pathologic ENE into microscopic or macroscopic ENE. To identify patients with a single nodal metastasis, we included patients with pathologic N1 stage tumors (based on *AJCC6* and *AJCC7*) and confirmed that these patients were also coded as having a single metastatic LN according to the participant user file variable, Regional Lymph Nodes Positive.[13]

We identified 673 patients with pN2a HPV-negative HNSCC with ENE in a single LN smaller than 3 cm who had undergone primary margin-negative resection and adjuvant radiation therapy. We then excluded patients with missing vital status (n = 104), receipt of palliative care (n = 3), meta-

static disease at diagnosis (n = 5), or receipt of chemotherapy not concurrent with RT (defined by >14 days; n = 57), producing a final cohort of 504 patients.[15]

Study Variables

The primary end point was OS. The primary independent variable of interest was type of adjuvant therapy (RT vs CRT). Socioeconomic and demographic variables included sex, age, race/ethnicity, severity of comorbidity as measured by the Charlson-Deyo comorbidity score, insurance status, income level, educational level, metropolitan status, and geographic region; treatment-related variables included facility type, number of Commission on Cancer–accredited facilities involved in care, and RT type; and oncologic variables included primary tumor site and pathologic staging based on AJCC6 or AJCC7 guidelines, depending on the year of diagnosis. All patients received a form of external beam radiation therapy; this was categorized as 3-dimensional conformal or external beam radiation therapy not otherwise specified or intensity-modulated RT. The specific chemotherapeutic agent is not available within the NCDB,[13] but the number of agents (none, single, or multiple) is reported.

Statistical Analysis

Statistical analysis was conducted from September 1, 2019, to April 16, 2020. We used χ^2 or 2-sided Fisher exact tests to assess differences in categorical variables between groups (received adjuvant RT or CRT), depending on the pertinent sample size. Kaplan-Meier analysis was used to estimate the OS probability. Survival curves were compared between groups using log-rank tests. Cox proportional hazards regression models were used to identify variables associated with OS. The proportional hazards assumption was met ($P > .05$). We first fit univariate Cox proportional hazards models to investigate the unadjusted associations between potential risk factors and OS, for which the above-mentioned study variables were used 1 at a time. A $P \leq .15$ was used as the initial variable selection criterion. Next, a multivariable Cox proportional hazards model with forward variable selection was used with variables that were significantly associated with OS from the univariate model. The final model included risk factors that were significantly associated with OS ($P < .05$ was the statistical significance level) as well as pertinent demographic variables (age, sex, race/ethnicity, and Charlson-Deyo comorbidity score). Risk of death attributed to the associated variables was expressed as hazard ratios (HRs) and corresponding 95% CIs.

To identify whether there were specific subpopulations that would differentially benefit from adjuvant CRT, we performed 2 planned subset analyses. First, to evaluate the efficacy of CRT among patients who would likely be candidates for cisplatin-based chemotherapy (and would most closely resemble participants in a clinical trial), we defined a subset based on age lower than 70 years and lack of comorbidity (Charlson-Deyo comorbidity score, 0). Second, to evaluate whether the efficacy signal for adjuvant CRT was only present in a relatively higher-risk group (ie, pT3/T4), we performed another subset analysis examining patients with AJCC7 pT3/T4 tumors. Finally, to ensure that our results were not due to unintended confounding by HPV-positive OPSCC cases that were classified as HPV-negative, we performed a sensitivity analysis excluding all cases of OPSCC. Subset and sensitivity analyses were performed using the same approach as the overall cohort. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc).

Results

Patient Characteristics

Of 504 patients with pN2a HPV-negative HNSCC with ENE who were treated with margin-negative surgery and adjuvant therapy, the mean age was 60.5 years (SD, 12.7 years); 319 (63.3%) were men, 185 (36.7%) were women, and 434 (86.1%) were White (**Table 1**). In total, 206 patients (40.9%) received adjuvant RT and 298 patients (59.1%) received adjuvant CRT. Relative to patients who received adjuvant CRT, patients who received adjuvant RT were more likely to be older than 70 years (35.4% vs 15.8%) and less likely to receive intensity-modulated RT (51.9% vs 62.4%). The 5-year OS of the overall cohort was 49.0%.

Adjuvant CRT vs RT in the Overall Cohort

The 5-year OS was similar for ENE-positive pN2a patients treated with adjuvant CRT and adjuvant RT on unadjusted Kaplan-Meier estimates (51% vs 47%; log-rank $P = .17$) (**Figure**). For the entire cohort, the results of univariate and multivariate Cox regression analyses are given in **Table 2**. On univariate analysis, adjuvant CRT was not associated with improved OS relative to adjuvant RT (HR, 0.83; 95% CI, 0.64-1.08). Using Cox multivariate regression analysis, adjuvant CRT was also not associated with improved OS relative to adjuvant RT (adjusted HR, 0.98; 95% CI, 0.74-1.30). The results were unchanged after sensitivity analysis excluded 28 patients with HPV-negative OPSCC on univariate (HR, 0.88; 95% CI, 0.68-1.15) and multivariate (adjusted HR, 0.93; 95% CI, 0.70-1.25) analyses (eTable 2 in the Supplement).

Adjuvant CRT vs RT in Subset Analyses

Planned subset analyses to identify whether specific subpopulations differentially benefited from adjuvant CRT showed that adjuvant CRT remained unassociated with improved OS. In the subset of 304 patients younger than 70 years with a Charlson-Deyo comorbidity score of 0, adjuvant CRT was not associated with improved OS relative to adjuvant RT on univariate analysis (HR, 1.08; 95% CI, 0.74-1.58) or multivariate analysis (adjusted HR, 0.98; 95% CI, 0.66-1.45) (**Table 3**). In the subset of 220 patients with AJCC7 pT3/T4 disease, adjuvant CRT was still not associated with improved OS relative to adjuvant RT on univariate analysis (HR, 0.87; 95% CI, 0.60-1.27) or multivariate analysis (adjusted HR, 1.03; 95% CI, 0.70-1.54).

Discussion

In this study, we used a robust national database with a precisely defined cohort of patients to show that for patients with

Table 1. Clinical and Demographic Characteristics of Included Patients

Characteristic	No. (%) of patients			*P* value
	Total patients (n = 504)	Adjuvant RT (n = 206)	Adjuvant CRT (n = 298)	
Age, y				
<50	90 (17.9)	22 (10.7)	68 (22.8)	<.001
50-59	143 (28.4)	41 (19.9)	102 (34.2)	
60-69	151 (30.0)	70 (34.0)	81 (27.2)	
≥70	120 (23.8)	73 (35.4)	47 (15.8)	
Sex				
Men	319 (63.3)	133 (64.6)	186 (62.4)	.62
Women	185 (36.7)	73 (35.4)	112 (37.6)	
Race				
White	434 (86.1)	177 (85.9)	257 (86.2)	.38
Black	39 (7.7)	19 (9.2)	20 (6.7)	
Other or unknown	31 (6.2)	10 (4.9)	21 (7.0)	
Insurance type				
Private	220 (43.7)	63 (30.6)	157 (52.7)	<.001
Medicaid	57 (11.3)	20 (9.7)	37 (12.4)	
Medicare	182 (36.1)	100 (48.5)	82 (27.5)	
Uninsured	23 (4.6)	11 (5.3)	12 (4.0)	
Other government or unknown	22 (4.4)	12 (5.8)	10 (3.4)	
Charlson-Deyo comorbidity score				
0	380 (75.4)	145 (70.4)	235 (78.9)	.08
1	95 (18.8)	48 (23.3)	47 (15.8)	
≥2	29 (5.8)	13 (6.3)	16 (5.4)	
Educational level[a]				
Highest quartile	113 (22.6)	42 (20.8)	71 (23.9)	.60
Second-highest quartile	157 (31.5)	60 (29.7)	97 (32.7)	
Second-lowest quartile	135 (27.1)	58 (28.7)	77 (25.9)	
Lowest quartile	9 4 (18.8)	42 (20.8)	52 (17.5)	
Median household income[a]				
Highest quartile	138 (27.7)	46 (22.8)	92 (31.0)	.18
Second-highest quartile	130 (26.1)	55 (27.2)	75 (25.3)	
Second-lowest quartile	133 (26.7)	55 (27.2)	78 (26.3)	
Lowest quartile	98 (19.6)	46 (22.8)	52 (17.5)	
Facility type[a]				
Community cancer program or integrated network	74 (15.5)	26 (12.7)	48 (17.6)	.28
Comprehensive community	122 (25.6)	57 (27.9)	65 (23.8)	
Academic or research	281 (58.9)	121 (59.3)	160 (58.6)	
No. of COC facilities				
1	382 (75.8)	158 (76.7)	224 (75.2)	.69
>1	122 (24.2)	48 (23.3)	74 (24.8)	
Region[a]				
Northeast	91 (19.1)	32 (15.7)	59 (21.6)	.43
South	142 (29.8)	64 (31.4)	78 (28.6)	
Midwest	183 (38.4)	80 (39.2)	103 (37.7)	
West	61 (12.8)	28 (13.7)	33 (12.1)	
Geography				
Metropolitan	378 (77.5)	143 (72.6)	235 (80.8)	.03
Nonmetropolitan	110 (22.5)	54 (27.4)	56 (19.2)	
Radiation type				
EBRT or 3-D conformal	211 (41.9)	99 (48.1)	112 (37.6)	.02
IMRT	293 (58.1)	107 (51.9)	186 (62.4)	

(continued)

Table 1. Clinical and Demographic Characteristics of Included Patients (continued)

Characteristic	No. (%) of patients			*P* value
	Total patients (n = 504)	Adjuvant RT (n = 206)	Adjuvant CRT (n = 298)	
No. of chemotherapy agents				
None	206 (40.9)	206 (100)	0	<.001
Single agent	227 (45.0)	0	227 (76.2)	
Multiagent	53 (10.5)	0	53 (17.8)	
Unknown	18 (3.6)	0	18 (6.0)	
Cancer primary site				
Oral cavity	370 (73.4)	143 (69.4)	227 (76.2)	.02
Oropharynx (HPV negative)	28 (5.6)	8 (3.9)	20 (6.7)	
Hypopharynx or larynx	106 (21.0)	55 (26.7)	51 (17.1)	
AJCC6/7 pathologic T category[a]				
T1 or T2	282 (56.2)	108 (52.7)	174 (58.6)	.19
T3 or T4	220 (43.8)	97 (47.3)	123 (41.4)	

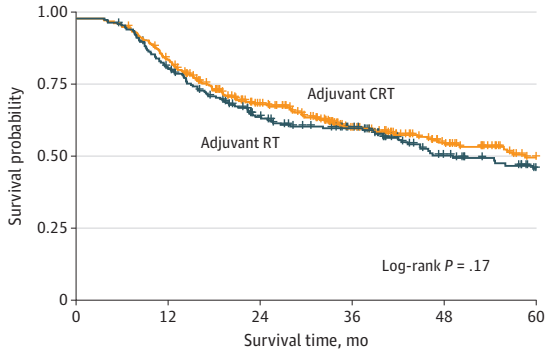
Abbreviations: 3-D, 3-dimensional; AJCC6/7, *American Joint Committee on Cancer Staging Manual*, edition 6 or 7; COC, Commission on Cancer; CRT, chemoradiation therapy; EBRT, external beam radiation therapy; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

[a] May not sum to total patient number owing to missing data.

HPV-negative HNSCC who had ENE in a single LN smaller than 3 cm (ie, AJCC8-defined pN2a disease) and who underwent margin-negative surgical resection, adding chemotherapy concurrent with adjuvant RT was not associated with improved OS. To our knowledge, this is the first study to examine the oncologic association of concurrent CRT in this clinical situation. The recommendation to add chemotherapy concurrent with adjuvant RT in patients with ENE is based on the results of 2 landmark RCTs (EORTC 22931 and ROTG 9501).[3,4] Since the publication of these trials, further precision and risk stratification within ENE-positive disease has occurred based on the number of ENE-positive LNs,[16-18] extent of ENE (ie, macroscopic vs microscopic),[16,19-23] and HPV status.[11,24-26] Because adding chemotherapy to adjuvant RT is associated with significant increases in acute- and late-treatment toxicity, it is important to precisely define which groups of patients benefit.[3-5] By showing that the addition of adjuvant chemotherapy in patients with pN2a HPV-negative HNSCC who had ENE and underwent margin-negative resection was not associated with improved OS, our study provides hypothesis-generating data that can be used to inform future investigation to help develop therapeutic protocols that maximize oncologic outcomes while minimizing treatment-related morbidity.

Our precisely defined cohort was chosen to identify a lower-risk ENE-positive HNSCC subgroup. First, there is growing evidence that the quantitative nodal burden of ENE-positive disease is associated with survival. Greenberg et al[16] showed that among patients with ENE, those with multiple positive lymph nodes have decreased disease-specific survival and OS relative to those with ENE who have only a single positive node. Other studies have found that single-node, ENE-positive disease has similar survival outcomes relative to single-node, ENE-negative disease.[17,18] Second, EORTC 22931 and RTOG 9501 did not separately examine the role of ENE on survival from other negative prognosticators, such as positive margins.[3,4] Therefore, we chose to include only patients receiving margin-negative surgery in our analysis. Finally, we further included a size criterion of LN disease to be smaller than 3 cm to examine a population that corresponds to the new staging criteria for pN2a disease. From these criteria, we identified a select population of patients with ENE-positive HNSCC who may not benefit from the addition of adjuvant chemotherapy to RT.

Figure. Kaplan-Meier Analysis of Overall Survival of Study Patients



No. at risk						
Adjuvant CRT	298	252	174	114	78	49
Adjuvant RT	206	167	118	96	61	43

All patients had human papillomavirus–negative head and neck squamous cell carcinoma, pathologic nodal category N2a with extranodal extension, and underwent adjuvant therapy with either chemoradiation (CRT) or radiation (RT).

The association between the extent of ENE and benefit from adjuvant CRT is unknown and is not addressed in the present study. Numerous studies have shown that more extensive, macroscopic ENE, defined as more than a 2-mm extension beyond the lymph node capsule,[6,27] confers a worse prognosis than microscopic ENE.[16,20,21] However, the prognostic significance of microscopic ENE remains contentious in both HPV-positive and HPV-negative HNSCC.[20,28] Unfortunately, we were unable to evaluate the role of the extent of ENE on survival. It is possible that patients with ENE-positive pN2a disease may disproportionately have microscopic ENE, confounding the association between the number of nodes with ENE and survival in this population. Future studies should explore the independent and conjoined effects of the number of nodes with ENE and the extent of ENE on prognosis and optimal adjuvant therapy.

Table 2. Association of Adjuvant CRT With Overall Survival[a]

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Adjuvant chemotherapy				
No (RT)	1 [Reference]		1 [Reference]	
Yes (CRT)	0.83 (0.64-1.08)	.17	0.98 (0.74-1.30)	.87
Age, y				
<50	1 [Reference]		1 [Reference]	
50-59	1.15 (0.75-1.76)	.52	1.07 (0.66-1.72)	.79
60-69	1.38 (0.91-2.07)	.13	1.20 (0.73-1.99)	.47
≥70	1.86 (1.23-2.81)	.003	1.53 (0.87-2.69)	.14
Sex				
Men	1 [Reference]		1 [Reference]	
Women	0.92 (0.70-1.21)	.54	0.86 (0.64-1.15)	.31
Race				
White	1 [Reference]		1 [Reference]	
Black	0.80 (0.47-1.34)	.39	0.64 (0.36-1.13)	.13
Other or unknown	0.86 (0.48-1.53)	.60	0.88 (0.49-1.61)	.69
Charlson-Deyo comorbidity score				
0	1 [Reference]		1 [Reference]	
1	1.25 (0.91-1.73)	.17	1.20 (0.85-1.69)	.30
≥2	1.60 (1.00-2.58)	.05	1.52 (0.91-2.55)	.11
Insurance type				
Private	1 [Reference]		1 [Reference]	
Medicaid	1.66 (1.09-2.52)	.02	1.97 (1.25-3.09)	.003
Medicare	1.78 (1.32-2.39)	<.001	1.32 (0.90-1.93)	.16
Uninsured	1.33 (0.69-2.57)	.39	1.41 (0.71-2.78)	.32
Other government or unknown	1.66 (0.89-3.12)	.11	1.31 (0.64-2.67)	.46
Educational level				
Highest quartile	1 [Reference]		Dropped out[b]	NA
Second-highest quartile	0.95 (0.67-1.35)	.79		
Second-lowest quartile	0.75 (0.52-1.09)	.14		
Lowest quartile	0.84 (0.56-1.26)	.41		
Median household income				
Highest quartile	1 [Reference]		Dropped out[b]	NA
Second-highest quartile	1.14 (0.80-1.63)	.46		
Second-lowest quartile	1.06 (0.74-1.53)	.74		
Lowest quartile	1.09 (0.74-1.61)	.67		
Facility type				
Community cancer program or integrated	1 [Reference]		Dropped out[b]	NA
Comprehensive community	1.14 (0.75-1.73)	.54		
Academic/research	0.94 (0.65-1.38)	.76		
Region				
Northeast	1 [Reference]		Dropped out[b]	NA
South	1.58 (1.05-2.37)	.03		
Midwest	1.27 (0.85-1.89)	.24		
West	1.42 (0.86-2.34)	.17		

(continued)

Table 2. Association of Adjuvant CRT With Overall Survival[a] (continued)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Geography				
Metropolitan	1 [Reference]		Dropped out[b]	NA
Nonmetropolitan	1.13 (0.83-1.54)	.44		
Type of RT				
EBRT or 3-D conformal	1 [Reference]		Dropped out[b]	NA
IMRT	0.99 (0.76-1.29)	.94		
Cancer primary site				
Oral cavity	1 [Reference]		1 [Reference]	
Oropharynx (HPV negative)	0.43 (0.19-0.97)	.04	0.51 (0.22-1.18)	.12
Hypopharynx or larynx	1.08 (0.80-1.46)	.61	0.74 (0.52-1.06)	.10
AJCC6/7 pathologic T category				
T1 or T2	1 [Reference]		1 [Reference]	
T3 or T4	1.50 (1.15-1.94)	.002	1.46 (1.08-1.97)	.01

Abbreviations: 3-D, 3-dimensional; AJCC6/7, *American Joint Committee on Cancer Staging Manual*, edition 6 or 7; CRT, chemoradiation therapy; EBRT, external beam radiation therapy; HPV, human papillomavirus; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; NA, not applicable; RT, radiation therapy.

[a] Assessed by univariate and multivariate Cox proportional hazards models.

[b] Dropped out of final multivariate model.

Because patients with several comorbidities or advanced age may be medically unfit for treatment intensification,[29,30] will likely not qualify for landmark RCTs,[3,4] and may be less likely to benefit from adjuvant CRT (particularly cisplatin-based),[31] we performed a subset analysis examining adjuvant CRT in patients younger than 70 years and with no comorbidities. Even in this subset of younger, healthier patients who would most likely tolerate cisplatin-based adjuvant CRT, we still found no benefit to adjuvant CRT over adjuvant RT associated with OS.

A second subgroup analysis was conducted in patients with pT3/T4 to evaluate whether the efficacy signal for adjuvant CRT might have been diluted by patients with pT1/T2 disease but still exists in this higher-risk, locally advanced disease group. However, the lack of survival benefit of CRT over RT in the higher-risk subset of patients with ENE-positive single LN smaller than 3 cm disease still held. To keep study findings concordant with current staging criteria (AJCC8), we attempted to reclassify the T category using criteria from the AJCC8 category strata for oral cavity (inclusion of depth of invasion, removal of extrinsic tongue muscle invasion from T4a). However, incomplete data about the depth of invasion and extent of soft tissue invasion for tumors of the oral cavity prevented us from accurately restaging these tumors. Although our findings suggest that even patients with an advanced T category may not benefit from treatment-intensification adjuvant CRT relative to adjuvant RT, future studies should confirm these findings in patients staged using the T categories based on AJCC8.

Given the clinical focus of this research, it is imperative to consider the practical question of how to apply our findings to clinical practice. Although our study did not find an OS benefit associated with adding chemotherapy concurrent with adjuvant RT for patients with ENE in a single LN, we believe that it is premature to suggest a change to clinical practice (ie, withholding chemotherapy) based on the results of this single study. As the de-escalation attempts for HPV-related oropharyngeal cancer treatment (on and off clinical protocol) have so clearly illustrated,[32-35] changing the standard of care is a multistep process fraught with method issues that require a convergence of evidence from numerous avenues (RCTs with tightly controlled, internally valid efficacy data and large-scale real-world studies outside of tightly controlled clinical trials showing clinical effectiveness).

Our preliminary findings, which are hypothesis-generating in nature, do suggest that additional research is a necessary and logical next step before clinical practice can be safely and ethically changed. The most definitive way to answer this clinical question would be through a multicenter RCT; however, an RCT targeting our cohort of interest may be neither feasible nor an optimal use of resources. Additional ways to investigate this clinical question include post hoc analyses of prior RCTs involving HNSCC treated with surgery and adjuvant therapy (eg, RTOG 9501, RTOG 0234, ROTG 0024, and EORTC 22931) that did not analyze this specific subgroup. Furthermore, because the AJCC now recognizes a separate staging category for pN2a disease based on a single node with ENE, future additional large-scale administrative studies should facilitate collection of key data for future analysis to corroborate these findings.

Finally, because OS remains poor for these patients, we should continue to seek alternative treatment paradigms that might intensify therapy beyond adjuvant radiation while avoiding the toxicity of cytotoxic chemotherapy that may not add a survival benefit. There are a number of ongoing clinical trials exploring the efficacy and tolerability of adjuvant radioimmunotherapy for patients with intermediate-risk HNSCC (NCT03700905 and NCT03383094).[36,37] Whether patients with ENE in a single LN would benefit from alternative noncytotoxic systemic therapies (such as adjuvant radioimmunotherapy) relative to adjuvant RT is thus an important question. Future intermediate-risk clinical trials might consider specifically enrolling patients with ENE in a single LN to identify whether they benefit from intensification with an adjuvant radioimmunotherapy paradigm.

Table 3. Association of Adjuvant Chemoradiation Therapy With Overall Survival Among 304 Patients Younger Than 70 Years With No Comorbidities and 220 Patients With pT3/T4 Disease Assessed by Multivariate Cox Proportional Hazards Model for Subset Analyses

	Patients <70 y with no comorbidities		Patients with pT3/T4 disease	
Variable	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Adjuvant chemotherapy				
No (RT)	1 [Reference]		1 [Reference]	
Yes (CRT)	0.98 (0.66-1.45)	.91	1.03 (0.70-1.54)	.87
Age, y				
<50	1 [Reference]		1 [Reference]	
50-59	0.98 (0.58-1.66)	.94	1.12 (0.52-2.39)	.77
60-69	1.15 (0.68-1.93)	.61	1.55 (0.75-3.21)	.24
≥70			1.78 (0.83-3.84)	.14
Sex				
Men	1 [Reference]		1 [Reference]	
Women	1.00 (0.68-1.49)	.97	0.80 (0.52-1.21)	.29
Race				
White	1 [Reference]		1 [Reference]	
Black	1.02 (0.46-2.24)	.96	1.02 (0.54-1.93)	.96
Other or unknown	1.80 (0.89-3.64)	.10	0.78 (0.34-1.81)	.57
Charlson-Deyo comorbidity score				
0	Dropped out[a]	NA	1 [Reference]	
1			0.99 (0.62-1.58)	.96
≥2			1.59 (0.80-3.15)	.18
Insurance type				
Private	Dropped out[a]	NA	Dropped out[a]	NA
Medicaid				
Medicare				
Uninsured				
Other government or unknown				
Educational level				
Highest quartile	Dropped out[a]	NA	Dropped out[a]	NA
Second-highest quartile				
Second-lowest quartile				
Lowest quartile				
Median household income				
Highest quartile	Dropped out[a]	NA	Dropped out[a]	NA
Second-highest quartile				
Second-lowest quartile				
Lowest quartile				
Facility type				
Community cancer program or integrated	Dropped out[a]	NA	Dropped out[a]	NA
Comprehensive community				
Academic or research				
Region				
Northeast	Dropped out[a]	NA	Dropped out[a]	NA
South				
Midwest				
West				
Geography				
Metropolitan	Dropped out[a]	NA	Dropped out[a]	NA
Nonmetropolitan				

(continued)

Table 3. Association of Adjuvant Chemoradiation Therapy With Overall Survival Among 304 Patients Younger Than 70 Years With No Comorbidities and 220 Patients With pT3/T4 Disease Assessed by Multivariate Cox Proportional Hazards Model for Subset Analyses (continued)

	Patients <70 y with no comorbidities		Patients with pT3/T4 disease	
Variable	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Type of RT				
EBRT or 3-D conformal	Dropped out[a]	NA	Dropped out[a]	NA
IMRT				
Cancer primary site				
Oral cavity	Dropped out[a]	NA	Dropped out[a]	NA
Oropharynx (HPV negative)				
Hypopharynx or larynx				
AJCC6/7 pathologic T category				
T3	1 [Reference]		Dropped out[a]	NA
T4	1.51 (1.03-2.21)	.04		

Abbreviations: 3-D, 3-dimensional; AJCC6/7, *American Joint Committee on Cancer Staging Manual*, edition 6 or 7; CRT, chemoradiation therapy; EBRT, external beam radiation therapy; HPV, human papillomavirus; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; NA, not applicable; RT, radiation therapy.

[a] Dropped out of final multivariate model.

Limitations

Although this was a methodologically rigorous study using a precisely defined cohort in a national sample of patients to address an ongoing area of clinical uncertainty, it has important limitations. In our final cohort of patients with pN2a HPV-negative HNSCC with ENE in a single LN smaller than 3 cm who had undergone primary margin-negative resection and adjuvant RT, 15% of potentially eligible cases were excluded owing to missing vital status. Although this is not uncommon for studies using the NCDB, incomplete data are often not missing at random; exclusion of these cases can lead to selection bias and affect study results and conclusions.[38-40] In addition, the reasons some patients received adjuvant CRT and others received adjuvant RT are unclear. Although we attempted to control for potential allocation bias through multivariable regression modeling, there is potential residual unmeasured confounding that could account for the lack of improved OS in the adjuvant CRT arm. In addition, it is possible that the lack of improved OS with adjuvant CRT is due to the use of less efficacious systemic agents (particularly cetuximab-based therapy).[34,41,42] We attempted to control for this potential confounding through the subset analysis restricted to patients younger than 70 years and with no comorbidities who would most likely have received standard of care, cisplatin-based therapy. Additional associated variables, such as smoking status, may influence outcomes but were not analyzed because they are not available in the NCDB. End points associated with recurrence or DFS are not available in the NDCB. The RTOG 9501[4] showed that adjuvant CRT improves locoregional control and DFS relative to adjuvant RT. Further investigation of whether the addition of chemotherapy concurrent with adjuvant RT may improve locoregional control or DFS in this patient population is therefore warranted. Furthermore, it is possible that we did not find a benefit from the addition of chemotherapy to RT because our study was underpowered. However, a post hoc power calculation using the effect size for DFS observed in RTOG 9501[4] yielded a sample size estimate of 518. Thus, our sample size of 504 patients suggests that our findings of the lack of benefit of adjuvant CRT are not likely due to a type II error. Finally, it is possible that the extent of ENE may moderate the association between chemotherapy and survival for patients with pN2a HNSCC. Unfortunately, the extent of ENE (microscopic vs macroscopic) was missing or unknown for the majority of patients in the current study, preventing us from analyzing whether the association of CRT with survival is moderated by the extent of ENE. Future research should seek to clarify whether the role of adjuvant CRT for HPV-negative disease varies depending on whether the ENE is macroscopic or microscopic.

Conclusions

In summary, for patients with HPV-negative HNSCC who underwent margin-negative surgical resection and had ENE in a single LN smaller than 3 cm (ie, AJCC8-defined pN2A disease), adding chemotherapy concurrent with adjuvant radiation was not associated with improved OS in this study. Overall survival remains poor in this patient population. As a result, additional research is needed to identify the optimal therapeutic paradigm to minimize treatment toxicity while optimizing oncologic outcomes.

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REFERENCES

1. Chow LQM. Head and neck cancer. *N Engl J Med*. 2020;382(1):60-72. doi:10.1056/NEJMra1715715

2. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers*. National Comprehensive Cancer Network; 2019.

3. Bernier J, Domenge C, Ozsahin M, et al; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350(19):1945-1952. doi:10.1056/NEJMoa032641

4. Cooper JS, Pajak TF, Forastiere AA, et al; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350(19):1937-1944. doi:10.1056/NEJMoa032646

5. Kearney A, Cavanagh PW. Acute and long-term effects of chemoradiation therapy in head and neck cancer. In: Doyle PC, ed. *Clinical Care and Rehabilitation in Head and Neck Cancer*. Springer International Publishing; 2019:331-349. doi:10.1007/978-3-030-04702-3_20

6. American Joint Committee on Cancer. *AJCC Cancer Staging Manual, Eighth Edition*. Published 2018. Accessed July 7, 2019. https://cancerstaging.org/references-tools/deskreferences/Pages/default.aspx

7. Dünne AA, Müller HH, Eisele DW, Kessel K, Moll R, Werner JA. Meta-analysis of the prognostic significance of perinodal spread in head and neck squamous cell carcinomas (HNSCC) patients. *Eur J Cancer*. 2006;42(12):1863-1868. doi:10.1016/j.ejca.2006.01.062

8. American College of Surgeons. National cancer database. Published 2020. Accessed July 7, 2020. https://www.facs.org/quality-programs/cancer/ncdb

9. Janz TA, Graboyes EM, Nguyen SA, et al. A comparison of the NCDB and SEER database for research involving head and neck cancer. *Otolaryngol Head Neck Surg*. 2019;160(2):284-294. doi:10.1177/0194599818792205

10. World Health Organization. *International Classification of Diseases for Oncology, 3rd edition* (*ICD-O-3*). Accessed July 6, 2020. https://www.who.int/classifications/icd/adaptations/oncology/en/

11. An Y, Park HS, Kelly JR, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Cancer*. 2017;123(14):2762-2772. doi:10.1002/cncr.30598

12. Sinha P, Kallogjeri D, Gay H, et al. High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. *Oral Oncol*. 2015;51(5):514-520. doi:10.1016/j.oraloncology.2015.02.098

13. American College of Surgeons. Participant User Files. NCDB PUF data dictionary. Published 2016. Accessed July 13, 2020. https://www.facs.org/quality-programs/cancer/ncdb/puf

14. Collaborative Stage Data Collection System. Schema. Published 2020. Accessed July 6, 2020. https://cancerstaging.org/cstage/schema/Pages/version0205.aspx.

15. Amini A, Jones BL, McDermott JD, et al. Survival outcomes with concurrent chemoradiation for elderly patients with locally advanced head and neck cancer according to the National Cancer Data Base. *Cancer*. 2016;122(10):1533-1543. doi:10.1002/cncr.29956

16. Greenberg JS, Fowler R, Gomez J, et al. Extent of extracapsular spread: a critical prognosticator in oral tongue cancer. *Cancer*. 2003;97(6):1464-1470. doi:10.1002/cncr.11202

17. García J, López M, López L, et al. Validation of the pathological classification of lymph node metastasis for head and neck tumors according to the 8th edition of the TNM Classification of Malignant Tumors. *Oral Oncol*. 2017;70:29-33. doi:10.1016/j.oraloncology.2017.05.003

18. de Juan J, García J, López M, et al. Inclusion of extracapsular spread in the pTNM classification system: a proposal for patients with head and neck carcinoma. *JAMA Otolaryngol Head Neck Surg*. 2013;139(5):483-488. doi:10.1001/jamaoto.2013.2666

19. Matsumoto F, Mori T, Matsumura S, et al. Prognostic significance of surgical extranodal extension in head and neck squamous cell carcinoma patients. *Jpn J Clin Oncol*. 2017;47(8):699-704. doi:10.1093/jjco/hyx055

20. Wreesmann VB, Katabi N, Palmer FL, et al. Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. *Head Neck*. 2016;38(suppl 1):E1192-E1199. doi:10.1002/hed.24190

21. Shaw RJ, Lowe D, Woolgar JA, et al. Extracapsular spread in oral squamous cell carcinoma. *Head Neck*. 2010;32(6):714-722. doi:10.1002/hed.21244

22. Brasilino de Carvalho M. Quantitative analysis of the extent of extracapsular invasion and its prognostic significance: a prospective study of 170 cases of carcinoma of the larynx and hypopharynx. *Head Neck*. 1998;20(1):16-21. doi:10.1002/(SICI)1097-0347(199801)20:1<16::AID-HED3>3.0.CO;2-6

23. Woolgar JA, Rogers SN, Lowe D, Brown JS, Vaughan ED. Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. *Oral Oncol*. 2003;39(2):130-137. doi:10.1016/S1368-8375(02)00030-1

24. Freitag J, Wald T, Kuhnt T, et al. Extracapsular extension of neck nodes and absence of human papillomavirus 16-DNA are predictors of impaired survival in p16-positive oropharyngeal squamous cell carcinoma. *Cancer*. 2020;126(9):1856-1872. doi:10.1002/cncr.32667

25. Shevach J, Bossert A, Bakst RL, et al. Extracapsular extension is associated with worse distant control and progression-free survival in patients with lymph node-positive human papillomavirus-related oropharyngeal carcinoma. *Oral Oncol*. 2017;74:56-61. doi:10.1016/j.oraloncology.2017.09.014

26. Kompelli AR, Morgan P, Li H, Harris W, Day TA, Neskey DM. Prognostic impact of high-risk pathologic features in HPV-related oropharyngeal squamous cell carcinoma and tobacco use. *Otolaryngol Head Neck Surg*. 2019;160(5):855-861. doi:10.1177/0194599818818446

27. College of American Pathologists. Protocol for the examination of specimens from patients with cancers of the lip and oral cavity, version 4.0.0.1. Published 2017. Accessed March 25, 2020. https://documents.cap.org/protocols/cp-headandneck-lip-oralcavity-17protocol-4001.pdf

28. Cramer JD, Ferris RL, Kim S, Duvvuri U. Primary surgery for human papillomavirus-associated oropharyngeal cancer: survival outcomes with or without adjuvant treatment. *Oral Oncol*. 2018;87:170-176. doi:10.1016/j.oraloncology.2018.10.039

29. VanderWalde NA, Fleming M, Weiss J, Chera BS. Treatment of older patients with head and neck cancer: a review. *Oncologist*. 2013;18(5):568-578. doi:10.1634/theoncologist.2012-0427

30. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26(21):3582-3589. doi:10.1200/JCO.2007.14.8841

31. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009;92(1):4-14. doi:10.1016/j.radonc.2009.04.014

32. Sinha P, Haughey BH, Kallogjeri D, Spitznagel EL, Piccirillo JF. The role of postoperative chemoradiation for oropharyngeal carcinoma: a critical appraisal revisited. *Cancer*. 2017;123(5):887-888. doi:10.1002/cncr.30480

33. Wirth LJ, Burtness B, Nathan CO, Grégoire V, Richmon J. Point/counterpoint: do we de-escalate

treatment of HPV-associated oropharynx cancer now? and how? *Am Soc Clin Oncol Educ Book*. 2019; 39(39):364-372. doi:10.1200/EDBK_238315

34. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. 2019;393(10166):40-50. doi:10.1016/S0140-6736(18)32779-X

35. Mehanna H, Robinson M, Hartley A, et al; De-ESCALaTE HPV Trial Group. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. 2019;393(10166): 51-60. doi:10.1016/S0140-6736(18)32752-1

36. Chemoradiation vs immunotherapy and radiation for head and neck cancer. ClinicalTrials.gov identifier: NCT03383094. Published 2019. Accessed July 6, 2020. https://clinicaltrials.gov/ct2/show/NCT03383094

37. Study of nivolumab alone or in combination with ipilimumab as immunotherapy vs standard follow-up in surgical resectable HNSCC after adjuvant therapy (IMSTAR-HN). ClinicalTrials.gov identifier: NCT03700905. Updated January 28, 2019. Accessed July 6, 2020. https://clinicaltrials.gov/ct2/show/NCT03700905

38. Boffa DJ. What's lost in what's missing: a thoughtful approach to missing data in the National Cancer Database. *Ann Surg Oncol*. 2019;26 (3):709-710. doi:10.1245/s10434-018-07130-9

39. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393

40. Jones EA, Shuman AG, Egleston BL, Liu JC. Common pitfalls of head and neck research using cancer registries. *Otolaryngol Head Neck Surg*. 2019;161(2):245-250. doi:10.1177/0194599819838823

41. Saraswathula A, Chen MM, Colevas AD, Divi V. Assessing care value for older patients receiving radiotherapy with or without cisplatin or cetuximab for locoregionally advanced head and neck cancer. *JAMA Otolaryngol Head Neck Surg*. 2019. doi:10.1001/jamaoto.2019.2381

42. Galloway TJ, Ridge JA. Treatment of head and neck cancer—sometimes, less is more. *JAMA Otolaryngol Head Neck Surg*. 2019;145(12):1167-1169. doi:10.1001/jamaoto.2019.3078