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Survival benefit of post-operative chemotherapy for intermediate-risk advanced stage head and neck cancer differs with patient age☆

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ABSTRACT

Objectives: The National Comprehensive Cancer Network (NCCN) guidelines state that surgical patients with advanced-stage head and neck cancer (HNC) and risk factors other than extranodal extension (ENE) or positive margins should consider post-operative chemoradiation (POCRT). The goal of our study was to determine if POCRT is associated with overall survival (OS) compared with post-operative radiation therapy (PORT) and whether this varies with patient age.

Material and Methods: We conducted a retrospective study of 5319 adult patients with stage III-IV HNC who received primary surgical treatment with POCRT or PORT in the National Cancer Database (2010–2013). Patients with distant metastases, ENE, and positive margins were excluded. Intermediate risk features included pT3-T4, pN2-N3 disease, and lymphovascular invasion. Our main outcome was overall survival (OS). Statistical analysis included chi-squared tests and Cox proportional hazards regressions.

Results: On multivariable analysis for non-oropharyngeal cancer patients < 70 years, POCRT was associated with improved OS for T1-4N2-3 disease (hazard ratio [HR], 0.73, 95% confidence interval [CI]; 0.58–0.93) but was not associated with OS for T3-4N0-1 disease (HR, 0.92; 95% CI, 0.71–1.19). For patients ≥70 years, POCRT was not associated with improved OS for patients with T1-4N2-3 disease (HR, 1.21; 95% CI, 0.79–1.86) or T3-4N0-1 disease (HR, 1.08; 95% CI, 0.71–1.65). For oropharyngeal cancer patients with HPV-positive disease, POCRT was associated with decreased OS (HR, 9.52; 95% CI, 2.38–38.08).

Conclusion: Chemoradiation may offer a survival benefit for non-oropharyngeal intermediate-risk advanced-stage HNC patients < 70 years of age with T1-4N2-3 disease, but may not benefit those ≥70 years of age or those with T3-4N0-1 disease.

Introduction

The National Comprehensive Cancer Network (NCCN) guidelines recommend that head and neck mucosal squamous cell carcinoma patients with extranodal extension (ENE) or positive margins should receive post-operative chemoradiation (POCRT) [1]. These guidelines are based on the results of two landmark randomized controlled trials that demonstrated that these high-risk patients have improved disease-free survival and progression-free survival when treated with POCRT compared with post-operative radiation therapy (PORT) alone [2–5]. The pooled population from the trials also demonstrated improved overall survival (OS) with POCRT [3].

However, there is limited data on the role of POCRT in patients with intermediate risk-features (pT3-T4 disease, pN2-N3 disease, nodal disease in neck levels 4 or 5, perineural invasion (PNI), or lymphovascular invasion (LVI)). No clinical trial has adequately assessed the survival benefit of adding adjuvant chemotherapy to this subgroup of patients. The current NCCN recommendation is that these patients should be considered for POCRT.

The purpose of our study was to evaluate the utilization of POCRT compared with PORT for intermediate-risk advanced head and neck cancer patients and determine if there is a survival benefit associated with POCRT. We hypothesize that POCRT is associated with improved overall survival (OS) in younger patients with intermediate-risk advanced head and neck cancer.

☆ A portion of this data was presented at the 2018 Multidisciplinary Head and Neck Cancers Symposium in Scottsdale, AZ.

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Material and methods

We utilized data from the National Cancer Database (NCDB) from January 1, 2010 to December 31, 2013. The NCDB includes data from over 1500 Commission on Cancer-accredited programs and includes over 70% of incident cases of cancer in the United States [6]. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society [6]. The data in the NCDB is de-identified and our study was granted an exemption from the Stanford University institutional review board.

Patients with head and neck cancer were identified using the *International Classification of Diseases for Oncology, Third Edition*, topography codes for oropharynx (C-09.0–09.1, C-09.8–09.9, C-10.0–10.4, C-10.8–10.9, C-14.2, C-02.4, and C-01.9), oral cavity (C-02.0–02.3, C-02.8–03.1, C-03.9–04.1, C-04.8–05.2, C-05.8–06.2, C-06.8–06.9), larynx (C-32.0–32.3, C-32.8–32.9), and hypopharynx (C-12.9–13.2, 13C.8–13.9). Patients with disease in the lip, pharynx-not otherwise specified, and overlapping lesion of the lip, oral cavity, and pharynx were excluded. We included 130,804 patients with surgically treated head and neck squamous cell carcinoma. We excluded oropharyngeal cancer patients who had an excisional biopsy, resulting in 120,857 surgical patients. We limited the analysis to 2010 to 2013 since those were the years during which ENE, LVI, and human papilloma virus (HPV) data were consistently collected. After excluding patients who had neoadjuvant therapy, positive margins, positive or unknown ENE status, and those who had palliative care or clinical/pathologic distant metastases, we had 18,819 patients. 7817 patients had post-operative external beam radiation and documented chemotherapy administration or lack of chemotherapy. We limited the analysis to Stage III and IV patients and excluded those with T1N1 and T2N1 disease, resulting in a final cohort of 5319 patients. 92.9% of our cohort received radiation therapy doses between 45 and 76 Gy. Due to limitations on the data available in the database, we were unable to adequately evaluate perineural invasion or involvement of level 4 and 5 lymph nodes, which are also considered adverse features in the NCCN guidelines.

Clinical and pathologic variables included site, pathologic T and N stage, hospital type, lymph node yield, HPV status, and LVI. Lymph node yield was grouped into 18 or more lymph nodes examined and < 18 lymph nodes examined. Pathologic staging was based on the American Joint Committee on Cancer 6th and 7th editions staging guidelines. HPV status was grouped as positive and negative. Hospital type was classified as academic centers and community/other, which includes non-academic community cancer programs.

Demographic variables included sex, race, age, insurance, comorbidities, and socioeconomic status. Age was classified into 4 groups including < 50, 50–59, 60–69, and ≥70 years. Race was categorized into white, black, and other. Comorbidities were categorized using the Charlson/Deyo comorbidity index into 0, 1, and 2. Insurance was labeled as not insured, private/managed care, Medicare/Medicaid, and unknown. Income and educational level were grouped into the highest quartile group and compared with all other quartiles.

Our main outcome was overall survival (OS) in years from the date of diagnosis to death. Patients were censored at the last date the patient was known to be alive or December 31, 2013, whichever came first.

We used the χ^2 test to analyze our categorical variables. Cox-proportional hazards regression analysis was used to identify factors associated with OS. Hazard ratios (HR) and 95% confidence intervals (95% CIs) were calculated for the strength of association. We also conducted a propensity score analysis in order to control for differences in allocation between patients who received PORT and those who received POCRT. A logistic regression was used to build a model predicting receipt of POCRT based on sex age, comorbidities, pathologic T stage, pathologic N stage, insurance status, and hospital type. This model was used to produce propensity scores and care was taken to ensure the covariates were balanced across both groups within propensity score blocks. The radius method with the caliper set to 0.05 was used to match patients who received POCRT to patients who received PORT. The degree of balance between the POCRT and PORT groups after propensity score matching was determined by standardized differences, which were < 0.2 for all covariates except for nodal stage. All tests were 2-sided, and a *P* value < .05 was considered to be statistically significant. Statistical analyses were performed using STATA/SE (version 14.2; StataCorp, College Station, TX, USA).

Table 1
Group 1 baseline characteristics.

	PORT		POCRT		P value
	N	%	N	%	
Group 1: Stage III and IV (exclude T1N1 and T2N1)[a]	3158	59.4	2161	40.6	
Group 2: T3-4, N0-1	1783	72.4	680	27.6	
Group 3: Any T, N2-3	1372	48.2	1476	51.8	
Site					< .001
Oropharynx	760	51.3	722	48.7	
Oral Cavity	1571	62.2	956	37.8	
Hypopharynx	74	50.0	74	50.0	
Larynx	753	64.8	409	35.2	
Sex					.13
Male	2284	58.7	1604	41.3	
Female	874	61.1	557	38.9	
Comorbidities					.006
0	2354	58.2	1691	41.8	
1	645	62.6	386	37.4	
2+	159	65.4	84	34.6	
Age					< .001
< 50	410	49.8	413	50.2	
50–59	1030	54.8	851	45.2	
60–69	1004	62.4	604	37.6	
70+	714	70.9	293	29.1	
Race					.86
White	2700	59.3	1855	40.7	
Black	311	58.7	219	41.3	
Other	120	60.9	77	39.1	
pT					< .001
T1	435	50.2	431	49.8	
T2	528	51.5	497	48.5	
T3	705	65.3	375	34.7	
T4	1490	63.5	858	36.5	
pN					< .001
N0	1426	74.8	480	25.2	
N1	357	64.1	200	35.9	
N2	1358	48.6	1434	51.4	
N3	14	25.0	42	75.0	
Income					.36
Low	1876	58.6	1324	41.4	
Highest quartile	1182	59.9	791	40.1	
Education					.19
Low	2038	58.5	1447	41.5	
Highest quartile	1019	60.4	668	39.6	
Insurance					< .001
Not insured	211	57.8	154	42.2	
Private/Managed Care	1292	56.0	1016	44.0	
Medicare/Medicaid	1599	62.5	960	37.5	
Unknown	56	64.4	31	35.6	
Hospital Type					< .001
Community/Other	887	53.9	759	46.1	
Academic	2031	63.0	1195	37.0	
LVI					< .001
None	2152	63.6	1230	36.4	
LVI present	586	49.8	590	50.2	
Unknown	420	55.2	341	44.8	
Lymph Node Yield					< .001
≥18 Lymph Nodes	2462	61.0	1573	39.0	
< 18 Lymph Nodes	557	53.7	481	46.3	

[a] Groups 2 and 3 do not add up exactly to Group 1 due to 8 T4 patients with missing N stage data.