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Treatment Sequence and Survival in Locoregionally Advanced Hypopharyngeal Cancer: A Surveillance, Epidemiology, and End Results–Based Study

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Abstract

Objectives/Hypothesis: The objective of this study was to examine the association between modality of primary treatment and survival among patients with locoregionally advanced hypopharyngeal cancer.

Study Design: Retrospective cohort.

Methods: There were 2,328 adult patients diagnosed with stage III or IV, M0, hypopharyngeal squamous cell carcinoma identified within the Surveillance, Epidemiology and End Results (SEER) registry (years 2004–2015). Patients who received primary chemoradiation (CRT) were compared to those who received surgery with either adjuvant radiation therapy (S + RT), or surgery with adjuvant CRT (S + CRT). The latter primary surgery group (S + Adj) was also analyzed collectively. Overall survival (OS) and disease-specific survival (DSS) were assessed using Kaplan-Meier analyses and Cox regression models using a propensity score to adjust for factors associated with treatment allocation.

Results: Median survival was 20 months (interquartile range [IQR] = 10–45) with CRT and 25 months (IQR = 10–47) with S + Adj ($P < .001$). S + Adj had higher-grade cancers and more advanced T staging ($P < .001$). S + CRT was associated with longer OS (hazard ratio [HR] = 0.70, 95% confidence interval [CI]: 0.59–0.84) and DSS (HR = 0.66, 95% CI: 0.54–0.82) after adjusting for age, gender, race, subsite, grade, and stage. S + RT was associated with longer DSS than CRT (HR = 0.75, 95% CI: 0.57–0.99) but not OS (HR = 0.82, 95% CI: 0.66–1.04). S + Adj was associated with longer DSS in T1/T2 disease ($P = .04$) and T4 disease ($P = .0003$), but did not reach significance among patients with T3 disease ($P = .06$).

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Conclusions: Among patients with advanced hypopharyngeal cancer reported in the SEER database, treatment with S + Adj was associated with longer DSS and OS compared to those treated with primary CRT.

Level of Evidence: 2b

Keywords

Hypopharynx; squamous cell carcinoma of the head and neck; hypopharyngeal neoplasms; pharyngectomy; laryngectomy

INTRODUCTION

Several landmark trials have demonstrated that organ preservation treatment employing cisplatin-based chemoradiation (CRT) for advanced laryngeal squamous cell cancer (SCC) resulted in a high rate of laryngeal preservation without sacrificing overall survival.^{1,2} Subsequent observational studies of laryngeal SCC have reported decreased survival, raising concerns that first-line CRT perhaps has a survival cost.³

First-line CRT has been extrapolated to hypopharyngeal SCC (HSCC) based on trials that included subjects with laryngeal SCC and HSCC.⁴⁻⁶ Similar to the findings in laryngeal cancer, recent retrospective studies of advanced stage HSCC have suggested a survival benefit to primary surgery compared to organ preservation.⁷ HSCC is diagnosed as stage IV in a majority of cases (59.1% vs. 26.8% in laryngeal SCC),⁸ and the 5-year survival is 33%, compared to 62% for laryngeal SCC.⁹ Because the impact of treatment on survival may differ in HSCC, the appropriate allocation of organ-preserving modalities in HSCC deserves scrutiny.

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry collects information for approximately 34% of the US population from 19 geographic regions.¹⁰ Prior studies of HSCC using SEER data have demonstrated a shift toward radiation therapy (RT) rather than surgical treatment since 1990, without an decline in 5-year survival.^{11,12} Conversely, other studies have suggested better survival for those treated with surgery compared to RT alone.¹²⁻¹⁴ Chemotherapy data were not available within the SEER registry previous to the SEER 18 release, and no prior SEER study has clearly examined the sequence of radiation therapy and surgery. Most studies combine primary surgery groups with those that received salvage surgery. The objective of this study was to examine the relationship between primary treatment and survival among patients with locoregionally advanced HSCC, specifically comparing outcomes between those treated with CRT versus those treated with initial surgery and adjuvant therapy (S + Adj). We hypothesized that S + Adj would be associated with a survival advantage when compared to primary CRT.

MATERIALS AND METHODS

Database and Inclusion/Exclusion Criteria

This study was exempted (45 CFR 46.102[f]) after institutional review board review. The SEER 18 database (seer.cancer.gov; RRID:SCR_003293)¹⁵ was interrogated using SEER*Stat.¹⁶ Subjects were selected using the following criteria (Fig. 1): subjects were included if diagnosed with HSCC as their first malignancy between 2004 and 2015.¹⁷ Staging was defined using the American Joint Committee on Cancer 6th or 7th edition staging manual based on year of diagnosis.^{18,19} Stage I or II disease or distant metastases (M1) were exclusions. Current standard of care for advanced stage HSCC is either concurrent CRT, surgery (partial or total laryngopharyngectomy), or induction chemotherapy followed by concurrent CRT or surgery.²⁰ Subjects who received treatment other than this standard of care were excluded.

Treatment Group

Subjects were included in the CRT group if they received both chemotherapy and RT and either no surgery or received surgery after RT. Subjects were included in the S + Adj therapy group if they received surgery prior to receiving RT (S + RT) or CRT (S + CRT).

Statistical Analyses

SEER*Stat was used to analyze trends in 5-year survival.¹⁶ All other analyses were carried out using Stata SE version 15.1 (stata.com, RRID:SCR_012763; StataCorp, College Station, TX).²¹ Bivariate associations between treatment groups were tested using analysis of variance or Kruskal-Wallis tests for continuous variables, and χ^2 tests for categorical variables. Lymph node staging was dichotomized at stage N2b ($N2b = 0$, $N2b = 1$) for the multivariable models. Insurance status was only available for cases from 2007 to 2015. Individuals over age 65 years at the time of diagnosis that were filed as uninsured were classified as Medicare-eligible due to known inaccuracies of this variable.²²

Survival Analyses

Overall survival (OS) was calculated using vital status and follow-up time from diagnosis date. Disease-specific survival (DSS) was calculated using the cause-specific death classification developed by Howlader et al.²³ Kaplan-Meier (KM) survival analyses and log-rank tests were used to assess and compare OS and DSS between groups. Univariable Cox regression analyses for both OS and DSS were performed to select variables for consideration in multivariable models. Multivariable Cox regression models of OS and DSS were built using a backward stepwise approach, with an exclusion criterion of P value .05 on likelihood ratio tests. Adjustments for age, race, and sex were included in the model a priori. Insurance was excluded from multivariable models a priori because data were missing for years 2004 to 2006 (24.9% of the cohort). First-order interactions of model components were tested using likelihood ratio tests ($\alpha = .05$). Confounding by excluded variables was assessed using a change in log hazards $>10\%$. After model building, the variable for tumor grade was included in the model of DSS for uniformity between models. The proportional

hazards assumption was assessed using log–log plots, observed versus expected plots, and goodness-of-fit tests.

Propensity Score Analysis

A propensity score (PS) was generated to balance covariates between the treatment groups to isolate treatment effects using the methods described by Garrido et al.²⁴ Variables considered for inclusion in the PS were age, year of diagnosis, race, the primary site, grade, T stage, N stage, and overall stage. A logistic regression model was built using a backward stepwise approach and an exclusion criterion of likelihood ratio test *P* values .05. The final PS included year of diagnosis, T stage, and summary stage. Balance of covariates between treatment groups was assessed using standardized differences and assessed within quintiles of the final PS. Maximum standardized differences for each variable within the quintiles of PS was defined as 25%. Multivariable Cox regression models were then reassessed with the inclusion of the PS.

Survival by Tumor Staging

KM survival curves and multivariable Cox regression models were reassessed, stratified by tumor staging. The PS was omitted because it contained T-stage data, and the overall stage was included in the models as a covariate.

Sensitivity Analyses

Sensitivity analyses were performed on the subcohort limited to those who received pharyngectomy and/or total laryngectomy (PL) in an attempt to eliminate subjects who were potentially misclassified to the surgery group when limited details of surgery were available. Additional sensitivity analyses are described and included as supplemental materials.

RESULTS

Study Population

There were 2,328 subjects evaluated, with a mean age of 61.95 years (± 9.88 years), who were predominantly male (83.3%), non-Hispanic white (68.8%), married (51.8%), and insured (93.9%). Most cancers arose from the pyriform sinus (55.0%). The treatment groups differed significantly by tumor grade, T stage, overall stage, and survival time. The most common T stage in the CRT group was T1/T2 (40.3%), whereas most of the patients in the S + RT and S + CRT groups had T4 disease (43.6% and 47.5%, respectively; $P < .0001$). There was a higher proportion of stage III disease in the CRT group (24.0%) than in the S + RT or S + CRT groups (20.3% and 17.2%, respectively; $P = .004$). The S + RT group had the highest proportion of stage IVA disease (72.9%), followed by S + CRT (68.3%), and finally CRT (60.7%; $P = .004$). Cohort characteristics are summarized in Table I.

The median survival in both the S + RT and S + CRT groups was 25 months (interquartile range [IQR] = 12–59 and IQR = 10–47, respectively). This survival was significantly higher than the median survival in the CRT group (20 months, IQR = 10–45; $P < .001$). At the time of censoring, 38.1% of the CRT group was alive, 47.8% had died of their cancer, and 14.1%

had died of other causes. In the S + Adj group, 43.3% were alive, 41.1% had died of their malignancy, and 15.6% had died of other causes.

5-Year Survival and Treatment Trends

The proportion of patients receiving each treatment within the study population was stable throughout the study period (Fig. 2A,B.). Trends in 5-year OS and DSS were relatively stable for all stages of HSCC (Fig. 2C). Among those diagnosed with stage III or stage IV (M0) disease, there had been a nonsignificant increase in OS and DSS (Fig. 2D).

Survival Analyses

The unadjusted probability of survival for the S + Adj group was higher than the CRT group. This difference was significant for both OS ($P = .0006$) and for DSS ($P = .0006$; Fig. 3A,B.). S + CRT was associated with the longest OS ($P = .0007$) and DSS ($P = .002$) compared to S + RT and CRT (Fig. 3C,D.). Univariable Cox regression found that site, tumor stage, overall stage, treatment, age, and race were all significantly associated with both OS and DSS (Supporting Table I). Covariates were balanced after PS matching (Supporting Table II).

Multivariable regression demonstrated that treatment with S + CRT was independently associated with a 29% reduction in risk of overall death compared to treatment with CRT, after adjustments for age, sex, race, ethnicity, tumor site, extracapsular spread, tumor grade, lymph node stage, and the PS (hazard ratio [HR] = 0.71, 95% confidence interval [CI]: 0.60–0.85, $P < .001$; Table II). Treatment with S + CRT was associated with a 32% lower risk of disease-specific death compared to CRT after adjustments for model components (HR = 0.68, 95% CI: 0.55–0.83, $P < .001$; Table II). S + RT was nonsignificantly associated with a reduced risk of overall death compared to CRT and significantly associated with lowered risk of disease-specific death (OS HR = 0.82, 95% CI: 0.65–1.03, $P = .08$; DSS HR = 0.74, 95% CI: 0.56–0.97, $P = .03$; Table II). Interestingly, non-Hispanic black race compared to non-Hispanic white race was independently associated with a 37% increased risk of overall death (HR = 1.37, 95% CI: 1.17–1.60, $P < .001$; Table II) and a 35% increased risk of disease-specific mortality after adjustments for model components (HR = 1.35, 95% CI: 1.13–1.61, $P = .001$; Table II).

Survival by Tumor Staging

Survival analyses were performed after stratifying by T staging. Unadjusted OS was increased for all groups that received S + Adj, but the difference did not reach significance among those with T3 disease ($P = .1733$; Fig. 4A–C.). Unadjusted DSS in T1/T2 disease was significantly longer among those who received S + Adj ($P = .0388$; Fig. 4B). Unadjusted DSS was significantly longer among those with T4 disease that received S + Adj as compared to CRT ($P = .0003$; Fig. 4F). Multivariable Cox regression models stratified by T stage found similar results. In T4 disease, treatment with S + Adj was associated with a significantly reduced risk of both disease-specific and overall death. In T3 disease, S + Adj had a nonsignificant 33% reduction in risk of disease-specific death (HR = 0.67, 95% CI: 0.44–1.02, $P = .06$; Supporting Table III) and a 20% reduction in risk of overall death (HR = 0.80, 95% CI: 0.57–1.12, $P = .19$; Supporting Table IV). In T1/T2, S + Adj was associated

with nonsignificant reductions in both risk of disease-specific and overall death (Supporting Tables III and IV).

Survival by Type of Initial Surgery

Several different surgical procedures were documented in the SEER registry (Supporting Table V). In the CRT group, only 2.4% of the subjects received surgery after radiation. In the S + Adj group, the recorded surgeries were heterogeneous, with 37.7% receiving limited procedures (partial pharyngectomy, local resection, laser resection), 51.6% receiving a total laryngectomy and total pharyngectomy, and 10.3% receiving other radical surgeries. Of those described as receiving local resection, 36.8% had evidence of neck dissection (Supporting Table VI). This discordance raised concern that some surgical procedures without curative intent may have been miscoded as primary surgical treatment. Therefore, subset sensitivity analyses were performed examining only patients who received either pharyngectomy, laryngectomy, or PL as a component of their surgical treatment ($n = 267$).

KM analysis comparing CRT to subjects that received PL + Adj found that surgery remained associated with a significantly longer unadjusted OS ($P = .001$; Fig. 5A) and DSS ($P = .001$; Fig. 5B). PL + CRT was associated with longer unadjusted OS when separated from PL + RT and compared to both PL + RT and CRT ($P = .001$; Fig. 5C). DSS showed a similar pattern ($P = .003$; Fig. 5D). Comparisons with CRT split into CRT and CRT + salvage PL found the latter was associated with the shortest unadjusted OS and unadjusted DSS (Fig. 5E,F). Multivariable Cox regression models of OS and DSS comparing PL + Adj to CRT supported an advantage with PL + Adj. Compared to primary CRT, PL + RT was associated with a nonsignificant 19% reduction in risk of overall death (OS HR = 0.81, 95% CI: 0.63–1.03, $P = .090$) and with a 27% significant reduction in risk of disease-specific death (DSS HR = 0.73, 95% CI: 0.54–0.99, $P = .040$; Supporting Table VII). PL + CRT was associated with a significant 31% reduction risk of overall death (OS HR = 0.71, 95% CI: 0.59–0.86, $P < .001$) and a significant 35% reduction in disease-specific death (DSS HR = 0.67, 95% CI: 0.53–0.83, $P < .001$; Supporting Table VII).

DISCUSSION

In this study of advanced HSCC, we analyzed SEER 18 data after carefully defining treatment groups with the best available data. We found that first-line surgical treatment was associated with a significant increase in both OS and DSS compared to CRT after adjustments for important confounders.

In our multivariable model, S + CRT was associated with significantly longer OS and DSS, whereas S + RT was associated with significantly longer DSS after multivariable adjustment and PS matching. S + RT was associated with a nonsignificant increase in OS. The lack of significance in this subgroup may be due to other latent confounding traits, such as comorbidity burden, or perhaps the small number of subjects in the S + RT subgroup limited our ability to detect a survival advantage.

We explored the relationship between tumor stage, treatment, and survival. After stratification by stage, DSS was significantly longer among patients with T1/T2 or T4

disease who received primary surgery. Our findings support the current guidelines, which favor S + Adj over CRT for T4a disease,²⁰ as multivariable analyses demonstrated that S + Adj was associated with a significantly longer DSS and OS among patients with T4 HSCCs. Among those with T3 disease, S + Adj was associated with nonsignificantly reduced hazards for both OS and DSS. Though not significant, our results may be clinically meaningful. Primary CRT may offer organ and function preservation with acceptable survival and remains an important consideration when discussing goals of treatment for patients with stage T3 HSCC. Notably, T3 disease made up the smallest proportion of our cohort compared to T1/T2 and T4 disease, which limits the detection of a possible survival advantage for S + Adj in this subgroup.

In T1/T2, S + Adj was associated with a significant reduction in unadjusted risk of disease-specific death; however, after multivariable adjustment, S + Adj was associated with nonsignificant reductions of risk of both disease-specific and overall death. There is an emerging role of new surgical methods in management of early-stage HSCC. Transoral robotic surgery for HSCC has shown promising results, with DSS as high as 74.7% at 3 years.^{25–27} Transoral laser microsurgery has also been associated with a 5-year OS reported between 41% and 64%.^{28,29} New organ-preserving surgical approaches for patients with early T-stage tumors may allow identification of high-risk patients who require adjuvant CRT. Future studies are necessary to clarify the true benefits for these approaches.

Of the subjects designated as receiving surgery before radiation within SEER, 37.7% were listed as receiving local or limited surgeries. Our sensitivity analysis limited surgery to PL, and S + Adj treatment remained associated with improved survival compared to CRT. Notably, the rate of PL recorded in SEER after CRT was only 2.4% in this cohort. Review of Radiation Therapy Oncology Group 91–11 at 10 years found the incidence of salvage laryngectomy in laryngeal SCC to be 18.3% after concurrent CRT.^{2,30,31} Past comparisons of SEER data with Medicare claims have found a 90% concordance rate for surgeries and an 80% concordance rate for radiation therapy.^{32,33} SEER only records treatments delivered at a single institution, and only records treatment rendered as part of the initial management plan, perhaps creating a source of bias.

Our results are similar to the findings of other retrospective studies. Tassler et al.⁷ reviewed the outcomes of 137 patients with advanced HSCC and observed a survival benefit with primary PL compared to primary CRT. Two recent studies^{11,12} reported improved survival with surgery and RT compared to either modality alone. Kuo et al.¹³ analyzed the National Cancer Database (NCDB) and reported that both surgery with either RT or CRT were associated with longer survival. A report by Kim and Lee¹⁴ using SEER data reported no significant differences in survival between subjects receiving CRT and the surgical group; however, the analysis did not consider the sequence of radiation and surgery and did not exclude subjects with history of past malignancy. Patients with surgery after CRT failure were included in the surgery subcohort, and as seen in our analyses, CRT with subsequent surgery was associated with poor survival. The analysis in our study was carefully designed to examine the relationship between primary treatment selection and survival.

There are intrinsic caveats specific to SEER data that introduce limitations to our study. SEER records include single-site information, and it is possible that some patients went to other facilities to receive treatments.⁸ It is impossible to assess for locoregional recurrence, distant metastasis, or second primaries as outcomes using SEER registry data. Treatment information in the SEER registry does not include information about radiation dosing, chemotherapy regimen, delays in treatment, or treatment dates. Therefore, we could not adjust for the timing of chemotherapy and differentiate between induction chemotherapy versus concomitant chemoradiation. Cause-specific death within SEER is determined using death certificate data and may contain inaccuracies.²³ Data on the reason a subject did not receive adjuvant radiation therapy are not available in SEER. Insurance status was significantly associated with survival in univariate analysis, and we considered using imputation methods for the 3 years for which insurance status was missing. However, there are concerns about the accuracy for this SEER variable,²² and there was no evidence that insurance status was different between the groups (Table I). Therefore, we excluded insurance from our multivariable models. In sensitivity analyses (see Supporting Table 11), the inclusion of insurance in the multivariable model did not alter our results. This study may be affected by selection bias due to latent confounding by these or other unmeasured variables.

Despite these limitations, it appears that primary treatment with surgery may benefit patients with HSCC if carefully employed. Future directions include using the larger NCDB to revisit the relationship of S + RT compared to CRT, explore the relationship of insurance with treatment and survival and the role of primary treatment in T3 disease, and to investigate organ-preserving surgical approaches for T1/T2 disease. Further well-designed prospective studies will be needed to establish a definitive benefit of one treatment modality over the other.

CONCLUSION

Our contemporary analyses of locoregionally advanced HSCC within the SEER database found that primary surgical treatment with adjuvant therapy was associated with improved survival compared to primary CRT. Careful allocation of primary surgery may optimize survival with risk-appropriate tailoring of adjuvant therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Selection of subject with overall stage III or stage IV hypopharyngeal squamous cell carcinoma diagnosed between 2004 and 2015 in the Surveillance, Epidemiology, and End Results (SEER) registry based upon treatments received. AJCC = American Joint Committee on Cancer; ICD-O-3 = *International Classification of Diseases for Oncology, 3rd Edition*; RT = radiation therapy.

Fig. 2.

Survival and treatment trends of patients with hypopharynx squamous cell carcinoma in the Surveillance, Epidemiology, and End Results registry. Survival estimates for the years 2010 and 2011 are for 48 months and 36 months, respectively, due to study cutoffs. (A) Proportion of patients with all stages of hypopharynx squamous cell carcinoma receiving chemotherapy and radiation therapy (CRT), surgery with adjuvant radiation therapy, or surgery with adjuvant chemotherapy and radiation therapy. (B) Proportion of patients with stages III and IV (M0) disease receiving each treatment. (C) Trends in 5-year survival for all stages of hypopharyngeal cancer diagnosed between 2004 and 2011. (D) Trends in 5-year survival for stage III (M0) or stage IV (M0) disease. RT = radiation therapy.

Fig. 3.

Survival of patients with stage III and stage IV hypopharyngeal squamous cell carcinoma diagnosed between 2004 and 2015 in the Surveillance, Epidemiology, and End Results registry. Patients are grouped by recorded treatment received. (A) Overall survival (OS). (B) Disease-specific survival (DSS). (C) OS with surgery plus adjuvant treatment (S + Adj) split into surgery with adjuvant radiation therapy (S + RT) or adjuvant chemoradiation (S + CRT). (D) DSS with S + Adj split into S + RT and S + CRT. CRT = chemoradiation.

Fig. 4.

Kaplan-Meier survival analysis stratified by tumor staging characteristics among cohort of subjects with overall stage III and stage IV hypopharyngeal squamous cell carcinoma diagnosed between 2004 and 2015 in the Surveillance, Epidemiology, and End Results registry. Chemoradiation (CRT) was defined as primary radiation and chemotherapy. S + Adj was defined as primary surgery with adjuvant CRT or adjuvant radiation therapy. (A) Demonstrates overall survival (OS) among subjects with T1/T2 disease. (B) Demonstrates disease-specific survival (DSS) among subjects with T1/T2 disease. (C) OS in T3 disease. (D) DSS in T3 disease. (E) OS in T4 disease. (F) DSS in T4 disease.

Fig. 5.

Kaplan-Meier survival analyses among only those who received pharyngectomy and laryngectomy as their initial surgery. Comparisons of probability of overall survival (OS) were made between those receiving chemoradiation (CRT) as initial treatment and those receiving pharyngectomy and/or laryngectomy with adjuvant chemoradiation or adjuvant radiation therapy (PL + Adj). (A) OS was then compared between CRT, pharyngectomy, and/or laryngectomy with adjuvant CRT (PL + CRT) and pharyngectomy and/or laryngectomy with adjuvant RT (PL + RT). (C) OS was also compared with those receiving CRT and salvage radical pharyngectomy (CRT + S) separate from those managed with CRT

and no surgical interventions. (B) Disease-specific survival (DSS) comparing CRT with P +Adj. (D) DSS comparing CRT with PL+CRT and PL+RT. (F) DSS comparing CRT, PL +CRT, PL+RT, and CRT+S.

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Characteristics of Selected Cohort of Patients With Stage III or IV (MO) Hypopharyngeal Squamous Cell Carcinoma Diagnosed Between 2004 and 2015 in the Surveillance, Epidemiology, and End Results Database. *

TABLE I.

Characteristics [†]	CRT, n = 1,892	Surgery + RT, n = 133	Surgery + CRT, n = 303	Total, n = 2,328	P Value [‡]
Age	61.95 ± 9.96	64.30 ± 10.16	60.89 ± 9.02	61.95 ± 9.88	.004 [§]
Sex					.54
Female	316(16.7%)	18 (13.5%)	54 (17.8%)	388 (16.7%)	
Male	1,576 (83.3%)	115 (86.5%)	249 (82.2%)	1,940 (83.3%)	
Race and ethnicity					.089
NHW	1,297 (68.6%)	96 (72.2%)	209 (69.0%)	1,602 (68.8%)	
NHB	326 (17.2%)	21 (15.8%)	37 (12.2%)	384 (16.5%)	
NHO	125 (6.6%)	5 (3.8%)	30 (9.9%)	160(6.9%)	
Hispanic	144 (7.6%)	11 (8.3%)	27 (8.9%)	182 (7.8%)	
Marital status					.49
Single	445 (25.0%)	32 (25.2%)	63 (22.1%)	540 (24.7%)	
Married	911 (51.2%)	72 (56.7%)	152 (53.3%)	1,135(51.8%)	
Divorced/widowed	422 (23.7%)	23 (18.1%)	70 (24.6%)	515(23.5%)	
Insurance [¶]					.26
Uninsured	78 (5.4%)	1 (1.3%)	11 (4.7%)	90(5.1%)	
Insured	1,345 (93.5%)	73 (97.3%)	223 (95.3%)	1,641 (93.9%)	
Medicare eligible	16(1.1%)	1 (1.3%)	0 (0.0%)	17(1.0%)	
Primary site					.22
Pyrriform sinus	1,022 (54.0%)	84 (63.2%)	174(57.4%)	1,280 (55.0%)	
Posterior region	45 (2.4%)	2 (1.5%)	4 (1.3%)	51 (2.2%)	
Aryepiglottic fold	105 (5.5%)	4 (3.0%)	20 (6.6%)	129(5.5%)	
Posterior wall	124 (6.6%)	5 (3.8%)	17 (5.6%)	146(6.3%)	
Overlapping lesion	65 (3.4%)	1 (0.8%)	14 (4.6%)	80 (3.4%)	
Hypopharynx, NOS	531 (28.1%)	37 (27.8%)	74 (24.4%)	642 (27.6%)	
Grade					<.001 [§]
Grade I	64 (3.4%)	1 (0.8%)	10 (3.3%)	75 (3.2%)	

Characteristics [†]	CRT, n = 1,892	Surgery + RT, n = 133	Surgery + CRT, n = 303	Total, n = 2,328	P Value [‡]
Grade II	752 (39.7%)	67 (50.4%)	124 (40.9%)	943 (40.5%)	
Grade III	593 (31.3%)	54 (40.6%)	139 (45.9%)	786 (33.8%)	
Grade IV	19 (1.0%)	3 (2.3%)	4 (1.3%)	26 (1.1%)	
Unknown	464 (24.5%)	8 (6.0%)	26 (8.6%)	498 (21.4%)	
T stage					<.001 [§]
T1/T2	763 (40.3%)	47 (35.3%)	97 (32.0%)	907 (39.0%)	
T3	496 (26.2%)	28 (21.1%)	62 (20.5%)	586 (25.2%)	
T4	633 (33.5%)	58 (43.6%)	144 (47.5%)	835 (35.9%)	
N stage					.060
N0	251 (13.3%)	25 (18.8%)	34 (11.2%)	310 (13.3%)	
N1	465 (24.6%)	31 (23.3%)	70 (23.1%)	566 (24.3%)	
N2a	59 (3.1%)	2 (1.5%)	4 (1.3%)	65 (2.8%)	
N2b	128 (6.8%)	10 (7.5%)	19 (6.3%)	157 (6.7%)	
N2c	538 (28.4%)	45 (33.8%)	109 (36.0%)	692 (29.7%)	
N2, NOS	329 (17.4%)	18 (13.5%)	49 (16.2%)	396 (17.0%)	
N3	122 (6.4%)	2 (1.5%)	18 (5.9%)	142 (6.1%)	
Overall stage					.003 [§]
III	455 (24.0%)	27 (20.3%)	52 (17.2%)	534 (22.9%)	
IVA	1,148 (60.7%)	97 (72.9%)	207 (68.3%)	1,452 (62.4%)	
IVB	275 (14.5%)	8 (6.0%)	44 (14.5%)	327 (14.0%)	
IVNOS	14 (0.7%)	1 (0.8%)	0 (0.0%)	15 (0.6%)	
Survival, mo	20 (10–45)	25 (10–51)	25 (12–59)	21 (10–47)	.002 [§]

[§] Subjects were included in the chemoradiation group if they had radiation prior to any surgery plus chemotherapy. Subjects were included in the surgery with the adjuvant therapy group if they received primary surgery with either adjuvant radiation or adjuvant radiation and chemotherapy.

[†] Plus-minus values are mean ± standard deviation for normally distributed continuous variables. Values for nonnormal continuous variables are reported as median (interquartile range). Frequencies are reported as number (proportion of overall group within column).

[‡] Normally distributed continuous variables were assessed using an analysis of variance. Continuous variables with nonnormal distribution were assessed with the Kruskal-Wallis test. χ^2 tests were used to assess categorical variables.

[§] Statistically significant.

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Insurance status was stratified by age of 65 years due to known concerns about accuracy of insurance data. Subjects were classified as Medicare eligible if filed as uninsured but over the age of 65 years at the time of diagnosis. Insurance status was only available for the years 2007 to 2015 within the Surveillance, Epidemiology, and End Results database and was missing for 453 subjects in the CRT group, 59 in the S + RT group, and 69 in the S + CRT group.

CRT = chemoradiation; NHB = non-Hispanic black; NHO = non-Hispanic other; NHW = non-Hispanic white; NOS = not otherwise specified; S + CRT = surgery with adjuvant CRT; S + RT = surgery with adjuvant radiation therapy.

TABLE II.

Results of Multivariate Cox Regression of Both Overall Survival and Disease-Specific Survival in Selected Cohort of Patients With Stage III or IV (M0) Hypopharyngeal Squamous Cell Carcinoma in the Surveillance, Epidemiology, and End Results Database With Surgery Plus Adjuvant Therapy Split Into Adjuvant Chemoradiation or Adjuvant Radiation Therapy.*

	Overall Survival			Disease-Specific Survival		
	HR	95% CI	P Value	HR	95% CI	P Value
Age	1.02	1.01–1.03	<.001 [†]	1.02	1.01–1.03	<.001 [†]
Gender						
Female				1		
Male	1.05	0.90–1.23	.540	0.97	0.81–1.16	.726
Race						
NHW	1			1		
NHB	1.37	1.17–1.60	<.001 [†]	1.35	1.13–1.61	.001 [†]
NHO	0.92	0.72–1.18	.516	1.00	0.76–1.33	.987
Hispanic, all races	0.88	0.70–1.11	.267	0.95	0.73–1.23	.690
Primary site						
Pyriiform sinus	1			1		
Postcricoid region	1.33	0.92–1.92	.126	1.63	1.11–2.39	.012 [†]
Aryepiglottic fold	0.80	0.60–1.07	.130	0.82	0.59–1.14	.234
Posterior wall	1.16	0.92–1.46	.221	1.22	0.93–1.58	.150
Overlapping lesion	1.27	0.91–1.78	.153	1.30	0.89–1.91	.179
Hypopharynx, NOS	1.10	0.96–1.27	.166	1.15	0.98–1.34	.090
Grade						
Grade I	1			1		
Grade II	0.83	0.61–1.09	.177	0.72	0.53–0.98	.039 [†]
Grade III	0.72	0.54–0.96	.027 [†]	0.69	0.50–0.94	.020 [†]
Grade IV	0.82	0.45–1.43	.458	0.75	0.40–1.43	.390
Extracapsular spread	1.22	0.97–1.45	.085	1.34	1.08–1.67	.008 [†]
N stage						

	Overall Survival			Disease-Specific Survival		
	HR	95% CI	P Value	HR	95% CI	P Value
< N2b	1			1		
N2b+	1.18	1.09–1.39	.001 [‡]	1.36	1.18–1.56	<.001 [‡]
Propensity score	609	100–3689	<.001 [‡]	1634	207–12869	<.001 [‡]
Treatment [‡]						
CRT	1			1		
S + RT	0.82	0.65–1.03	.084	0.74	0.56–0.97	.032 [‡]
S + CRT	0.71	0.60–0.85	<.001 [‡]	0.68	0.55–0.83	<.001 [‡]

* Multivariable Cox regression models were built using a backward stepwise approach. The proportional hazards assumption and first-order interactions of all model components were tested.

[‡] Statistically significant.

[‡] Subjects were included in the CRT group if they had received primary radiation and chemotherapy. Subjects were included in the S + RT group if they received surgery with adjuvant radiation and the S + CRT group if they received surgery with adjuvant radiation and chemotherapy.

CI = confidence interval; CRT = chemoradiation; HR = hazard ratio; NHB = non-Hispanic black; NHO = non-Hispanic other; NHW = non-Hispanic white; NOS = not otherwise specified; S + CRT = surgery with adjuvant CRT; S + RT = surgery with adjuvant radiation therapy.