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Surgical vs Nonsurgical Treatment Modalities for T3 Glottic Squamous Cell Carcinoma

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Abstract

IMPORTANCE—Further investigation is needed in the outcomes of currently available treatment for T3 glottic squamous cell carcinoma (SCC), a unique type of laryngeal cancer.

OBJECTIVE—To compare overall survival (OS) and functional outcomes among patients with T3 glottic SCC receiving nonsurgical and surgical management.

DESIGN, SETTING, AND PARTICIPANTS—This secondary analysis used data from the Surveillance, Epidemiology, and End Results (SEER) registry and Medicare databases. All patients with T3 glottic SCC who received a diagnosis from January 1, 1992, to December 31, 2010, were included. Data were analyzed from April 2014 to August 2015.

INTERVENTIONS—Surgery with or without adjuvant radiotherapy and/or chemotherapy.

MAIN OUTCOMES AND MEASURES—Five-year OS and functional outcomes.

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH. This study used the linked Surveillance, Epidemiology, and End Results (SEER)–Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. Dr Piccirillo is the editor and Dr Kallogjeri is the statistics editor of *JAMA Otolaryngology–Head & Neck Surgery*. Neither was involved in the editorial evaluation or decision to accept this article for publication.

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RESULTS—Among the 487 patients identified with T3 glottic SCC (418 men [85.8%]; 69 women [14.2%]; median age, 74.3 [interquartile range, 70.4–80.6] years), the 5-year OS for nonsurgical management, surgery alone, and surgery plus adjuvant treatment were 36% (95% CI, 30%–42%), 41% (95% CI, 30%–53%), and 41% (95% CI, 32%–51%), respectively. Multivariable analyses revealed an adjusted hazard ratio for OS of 0.68 (95% CI, 0.49–0.94) for patients receiving surgery alone vs nonsurgical management and 0.75 (95% CI, 0.57–0.98) for patients receiving surgery plus adjuvant treatment vs nonsurgical management. Gastrostomy tube dependence was highest in patients receiving surgery plus adjuvant treatment (30 of 98 patients [30.6%]). Tracheostomy dependence was highest in patients receiving chemoradiotherapy (34 of 92 patients [37.0%]).

CONCLUSIONS AND RELEVANCE—Overall survival showed a statistically significant and clinically meaningful improvement in patients with T3 glottic SCC who underwent surgery compared with a nonsurgical treatment. Furthermore, the data suggest that adjuvant and nonsurgical treatment result in a dysfunctional larynx; however, this association needs further study.

Laryngeal cancer will account for approximately 13 000 new cases of cancer and 3500 deaths in the United States in 2015.^{1–4} In the United States, the male-to-female incidence ratio is 4:1. The main risk factors attributed to laryngeal cancer are tobacco and alcohol use. However, human papillomavirus (HPV) is linked to head and neck cancer, including laryngeal cancer.^{5–7}

Squamous cell carcinoma (SCC) accounts for 85% to 95% of all laryngeal malignant neoplasms.^{8,9} Laryngeal cancer can affect the supraglottis, glottis, and subglottis. Each subsite has specific tumor characteristics. Glottic SCC accounts for 51% of all laryngeal cancers.³ The 5-year survival for patients with laryngeal cancer has decreased minimally in the United States from 66% during the time from 1975 to 2000 to 63% during the time from 2004 to 2010.^{1–4}

Glottic SCC is unique.^{10–14} The glottis is lined by stratified squamous epithelium that covers the 3-layered lamina propria forming the vocal ligament, which has few lymphatic vessels. This special squamous epithelium, with the anatomic barriers in the glottis, explains the delayed regional spread of glottic SCC.⁹ In a series of 910 patients,¹⁵ cervical lymph node metastasis in glottic SCC was 5.9%, and only 18% of patients with T3 glottic SCC had positive cervical lymph node metastasis. Staging of glottic SCC follows the American Joint Committee on Cancer (AJCC) system.¹⁶ Tumors limited to the larynx with vocal-fold fixation, invasion of paraglottic space, and/or invasion of the inner cortex of the thyroid cartilage constitute T3 glottic cancer.

The goals of treatment for patients with laryngeal cancer are to cure cancer and preserve laryngeal function while minimizing treatment-associated morbidity. A functional larynx is defined by an understandable voice; the ability to swallow without gastrostomy tube supplementation, aspiration, or the presence of esophageal stricture; and the ability to breathe without a stoma or tracheostomy.

Treatment for T3 glottic SCC includes surgery with or without adjuvant treatment and nonsurgical management consisting of chemoradiotherapy (CRT).¹⁷ The surgical options include total laryngectomy or partial laryngectomy, including transoral laser microsurgery.^{18–20} Chemoradiotherapy was introduced in the early 1990s in an attempt to conserve the larynx, and research suggests comparable survival rates to total laryngectomy.¹¹ Although preserving the larynx is a very laudable goal, nonsurgical approaches can result in severe tissue damage and a preserved yet nonfunctional larynx. The change in the larynx appearance after nonsurgical management precludes follow-up by clinical examination and endoscopy, and the presence of persistent edema raises the suspicion of persistent cancer.^{20,21}

In previous research, all laryngeal cancers were studied as a single group, without separating outcomes by different subsites.^{10–12,22} Advanced laryngeal cancers, defined as stage III or IV, were studied as 1 group, although a very heterogeneous one owing to the upstaging that occurs with the presence of lymph nodes (ie, any palpable lymph node will upstage the tumor to stage III regardless of initial T stage). The objective of this study was to compare overall survival (OS) of patients with T3 glottic SCC treated by nonsurgical management, surgery, or surgery with adjuvant therapy using the Surveillance, Epidemiology, and End Results (SEER)–Medicare database. In addition, we sought to compare treatment-associated functional outcomes.

Methods

Data Source

A data set was obtained from the SEER registry linked with Medicare claims. SEER is a National Cancer Institute–sponsored program that includes data from population-based cancer registries that cover approximately 28% of the US population, with overrepresentation of minority populations.¹⁴ The linkage of SEER data and Medicare claims is a collaborative effort by the National Cancer Institute, the SEER registries, and the Centers for Medicare & Medicaid Services.¹⁴ This study was approved by the Human Research Protection Office at Washington University School of Medicine, who waived the need for informed consent.

Study Population

From a sample of 41 680 patients with head and neck cancer in the Patient Entitlement and Diagnosis Summary File (PEDSF) from SEER, we derived a cohort of 487 patients with T3 glottic SCC (Table 1). Glottic cancers were defined using the *International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)* site code 320. Similarly, *ICD-O-3* histology codes (8050–8084) were used to define squamous cell histology. We identified T3 tumors using AJCC 7th edition staging criteria.¹⁶ The SEER PEDSF data include AJCC stage information for 2004 and beyond; but for patients who received a diagnosis before 2004, the SEER variables for extent of disease were used to derive the T stage.¹⁶ Because comorbidity at the time of cancer diagnosis was assessed using Medicare files, our cohort included patients 66 years or older who had at least 1 full year of uninterrupted Parts A and B Medicare coverage before diagnosis. Patients enrolled in Medicare health maintenance

organizations in the year preceding the diagnosis were excluded from the analysis because claims were not generated. Patients with a diagnosis before January 1, 1992, or younger than 66 years were excluded, as were patients with a history of head and neck cancer or distant metastasis at the time of presentation or with a diagnosis at autopsy. Follow-up survival data were available through December 31, 2010.

Treatment

The SEER PEDSF data include information on surgical and radiotherapeutic (RT) management within the first 4 months of diagnosis. Surgical treatment was categorized as no surgery, local tumor excision, partial laryngectomy, or total laryngectomy with or without neck dissection. Radiotherapy was dichotomized as none or external beam RT. Medicare claims files were searched for chemotherapy (CT)-related claims within 90 days of diagnosis to identify patients receiving primary CT. The Medicare claims files searched included the Medicare Provider Analysis and Review (MEDPAR) file, the National Claims History (NCH) file, the Home Health Agency file, the Durable Medical Equipment file, and the outpatient (OUTPAT) file. Chemotherapy-related claims were identified using codes from the *International Classification of Diseases, 9th Revision (ICD-9)*, *Current Procedural Terminology* codes, and Healthcare Common Procedure Coding System (HCPCS) codes.

Covariates

Demographic covariates included patient age, sex, race, marital status, geographic region, and residence in metropolitan or nonmetropolitan counties. Comorbidity was identified using Medicare claims preceding diagnosis and was quantified using the Charlson Comorbidity Index.^{23–25} Inpatient claims from the MEDPAR file, physician claims from the NCH file, and outpatient claims from the OUTPAT file were used for the calculation of the Charlson Comorbidity Index. Nodal stage was directly available from PEDSF for patients who received a diagnosis in 2004 or later, and SEER extent-of-disease variables were used to derive the N stage in accordance with AJCC 7th edition criteria for patients who received a diagnosis before 2004. Additional covariates included a history of non-head and neck cancer and year of diagnosis.

Outcomes

Definitions—Our primary outcome was OS, defined as the time from diagnosis to death due to any cause. *Salvage total laryngectomy* was defined as a total laryngectomy performed after the primary treatment. Salvage total laryngectomies were identified using Medicare claims and the *ICD-9* procedural code for total laryngectomy. The median time to salvage surgery was defined as the time from the start of treatment to the date of the Medicare claim for total laryngectomy.

Functional Outcomes—Gastrostomy and tracheostomy dependence were investigated using *ICD-9* and HCPCS codes from Medicare claims files. The presence of a gastrostomy- or a tracheostomy-related claim more than 1 year after the start of treatment was considered an indication of gastrostomy or tracheostomy dependence. We used start of treatment as our time zero for these outcomes because we are examining the treatment-related morbidity. Because all patients who undergo laryngectomy have a permanent stoma, tracheostomy

dependence was only evaluated for patients who had nonsurgical management or who received primary surgery other than total laryngectomy. Cases of esophageal stricture were identified using *ICD-9* diagnostic and procedural codes from the Medicare claims files, and the time from treatment initiation to the first claim was recorded.

Statistical Analysis

Data were analyzed from April 2014 to August 2015. The distribution of covariates was explored using standard descriptive statistics. We used Kaplan-Meier plots to explore survival patterns and the log-rank test for comparison of survival among treatment groups. Cox proportional hazards regression was used for multivariable survival analysis. Variables significant in univariate analysis at the α level of .1 were included in multivariable analysis. In addition, variables that are associated with survival in head and neck cancer, including sex,²⁶ race,²⁶ and year of diagnosis,²⁷ were included in the multivariable model of OS independent of the observed significance.

In this observational study, patients were not randomized to different treatment modalities. We used the inverse probability of treatment weighting method to adjust for unmeasured confounders related to treatment assignment with the aim of approximating the results of this observational study with those of a randomized clinical trial.^{28,29} Inverse probability of treatment weighting uses a propensity score, which is the probability of receiving a treatment, given a set of covariates. Covariates used for propensity calculations from multinomial logistic regression included region, population density, year of diagnosis, age group, sex, race, marital status, comorbidity, and N stage. We assessed the covariate balance between treatment cohorts after inverse probability of treatment weighting.^{28,29}

The proportional hazards assumption was tested for all variables using both log-minus-log plots. The effect of treatment modality on survival was presented as an adjusted hazard ratio (aHR) with a 95% CI after weighting by the inverse probability of treatment and controlling for other variables. All tests of statistical significance were evaluated at the 2-sided α level of 0.05. We used SAS statistical software (version 9.3; SAS Institute Inc) for all analyses.

Results

Description of the Cohort

The cohort is described in detail in Table 2. Of 487 patients with T3 glottic SCC (418 men [85.8%]; 69 women [14.2%]; median age, 74.3 [interquartile range, 70.4–80.6] years), 258 received nonsurgical management, 75 received surgery alone, and 118 received surgery plus adjuvant treatment. Thirty-six patients received no treatment and were excluded from analysis. Median follow-up for the entire cohort was 27 (interquartile range, 11–61) months; among survivors, 46 (interquartile range, 27–81) months. Most patients who received a diagnosis before 2000 underwent primary surgery compared with those who received a diagnosis after 2000 (59 of 104 [56.7%] vs 134 of 347 [38.6%]).

Survival Analysis

The median OS for the entire cohort was 34 (95% CI, 26–42) months. The 5-year OS for nonsurgical management, surgery alone, and surgery plus adjuvant treatment were 36% (95% CI, 30%–42%), 41% (95% CI, 30%–53%), and 41% (95% CI, 32%–51%), respectively. Univariate analysis demonstrated OS to be significantly associated with age, being single, Charlson Comorbidity Index of 2 or more, and receiving nonsurgical management. Age, sex, comorbidity, nodal stage, and treatment remained significant in the multivariable Cox proportional hazards regression model.

A multivariable Cox proportional hazards regression model analysis run without propensity score weighting showed no significant association between treatment and OS, with HRs of 0.77 (95% CI, 0.55–1.08) for surgery alone compared with CT, RT, or CRT and 0.75 (95% CI, 0.56–1.01) for surgery plus RT or CRT compared with CT, RT, or CRT. The same model run in the propensity score–weighted sample showed that after controlling for age, sex, comorbidity, nodal stage, and treatment, patients receiving surgery alone had a 32% reduced risk for all-cause mortality compared with patients receiving nonsurgical management (aHR, 0.68; 95% CI, 0.49–0.94), and patients receiving surgery plus adjuvant treatment had a 25% reduced risk for all-cause mortality compared with those receiving nonsurgical management (aHR, 0.75; 95% CI, 0.57–0.98) (Table 3). The adjusted survival experience of patients in each treatment group is displayed in the Figure.

Salvage Total Laryngectomy

This analysis was conducted on 351 patients, after excluding 100 patients who received total laryngectomy as their primary treatment. A total of 46 procedures (13.1%) were salvage total laryngectomies. Median time to salvage surgery was 12 (range, 3–42) months. Among patients receiving nonsurgical management, 36 of 258 (14.0%) required a salvage total laryngectomy (19 received RT only, and 17 received CRT).

Gastrostomy and Tracheostomy Dependence

The prevalence of gastrostomy-related claims 1 year after the start of treatment among nonsurgical, surgical, and surgical plus adjuvant treatment groups were 39 of 189 (20.6%), 12 of 65 (18.5%), and 30 of 98 (30.6%), respectively ($\chi^2_2=4.56$; $P=.10$). The prevalence of tracheostomy-related claims 1 year after the start of treatment was not significantly different among patients receiving RT only (26 of 97 [26.8%]) vs CRT (34 of 92 [37.0%]) vs primary surgery (16 of 65 [24.6%]) ($\chi^2_1=1.178$; $P=.28$).

Esophageal Stricture

The prevalence of esophageal stricture in the cohort was 71 of 451 patients (15.7%). The prevalence among nonsurgical, surgical, and surgical plus adjuvant treatment groups was 26 of 258 patients (10.1%), 12 of 75 patients (16.0%), and 33 of 118 patients (28.0%), respectively. The median time to stricture from treatment start was 15 months. After controlling for age and comorbidity in a time-to-event analysis, surgery plus adjuvant treatment was found to have a statistically significant higher risk for esophageal strictures than the 2 other groups (aHR for surgery alone, 1.16 [95% CI, 0.58–2.3]; aHR for surgery

plus adjuvant treatment, 2.32 [95% CI, 1.37–3.91]; nonsurgical management was the reference category).

Discussion

In this study, we found that our primary outcome of OS demonstrated statistically significant and clinically meaningful improvement in patients who underwent primary surgery, with or without adjuvant therapy after propensity score weighting. We found no clear evidence of improved functional outcomes associated with any treatment method. The likelihood of a salvage laryngectomy was highest in patients receiving initial nonsurgical management, whereas gastrostomy dependence was highest among patients receiving surgery plus RT. Tracheostomy dependence was highest among patients receiving CRT. The highest prevalence of esophageal stricture was among patients receiving surgery plus adjuvant treatment.

In previous studies, the 5-year survival outcomes of patients with laryngeal cancer were comparable between surgical and nonsurgical groups, with no statistically significant difference suggesting a better treatment.^{10–12,22} However, nonsurgical management was preferred owing to the notion of organ preservation. The Department of Veterans Affairs (VA) Laryngeal Cancer Group performed the landmark study that shifted the trend of laryngeal cancer treatment toward nonsurgical management.¹¹ The VA Laryngeal Cancer Group demonstrated that survival after nonsurgical therapy is comparable to survival after total laryngectomy with reasonable laryngeal preservation. The Radiation Therapy Oncology Group trial 91–11 was designed to determine the best treatment sequence and found better survival and laryngeal preservation with CRT than other nonsurgical options.²² Since then, CRT has been a candidate for the treatment of choice for advanced laryngeal cancer.^{30,31}

The rate of salvage total laryngectomy in the nonsurgical management group of this cohort was lower than in previous literature. Ascertainment of the indication for salvage laryngectomy, whether recurrence or functional, is difficult in this cohort. The VA study reports a 35% rate of salvage laryngectomy among patients with stages III and IV laryngeal cancer receiving CT.¹¹ The issue with studies grouping the different stages of laryngeal cancer is that they grouped all subsites of laryngeal cancer in a single category, although glottic cancers have been shown to usually have a different behavior. In addition, stages III and IV were considered advanced laryngeal cancers, but they contained a variety of different tumor sizes and lymph node involvement.¹⁶ We believe that the T3 group of glottic cancers represents a distinct subset of laryngeal cancers with a moderate tumor load that requires a more individualized approach to treatment.

The assessment of laryngeal function is difficult to extrapolate from the SEER-Medicare database. Most previous studies looked at larynx preservation vs larynx function, although the morbidity risk associated with either treatment option is important. With CRT, the deterioration in swallowing is usually of long duration and progressive owing to edema, reduced sensation, and long-term fibrotic changes that markedly affect functioning.^{20,21} A comparison of functional outcomes from previous studies is difficult because the assessment measures were not standardized.^{18,19,32,33}

In our study, we chose tracheostomy and gastrostomy tube dependence for more than 1 year after the start of treatment as an indication of larynx function. Tracheostomy dependence indicated significant alteration of the normal airway, which precluded decannulation. Gastrostomy dependence indicated significant swallowing dysfunction that required supplementation through a gastrostomy tube. Tracheostomy tube dependence was higher among patients receiving CRT, which may reflect more severe tissue damage caused by adding CT. Two independent studies^{32,33} found that patients with advanced laryngeal cancer receiving RT or surgery had minimal swallowing problems; however, they had worse swallowing outcomes if they received CRT and CRT plus surgery.

Esophageal strictures were indicators of treatment complications. The prevalence of esophageal strictures was highest among the group receiving surgery plus adjuvant treatment. These findings are consistent with those of Francis et al,³⁴ who found that patients who receive combined surgery plus adjuvant treatment more commonly experienced stricture. This finding may be related to the extent of tissue fibrosis or cricopharyngeal dysfunction resulting from surgery, and/or greater global neuromuscular tissue damage caused by CRT. An increased risk for esophageal strictures in patients receiving surgery and adjuvant treatment posits the argument for de-escalation of adjuvant therapies for individualized patients based on their tumor extent and characteristics and the clearance of surgical margins.³⁵ This proposal is further supported by our observation that identical 5-year OS was recorded in both primary surgical groups, with or without adjuvant treatment.

This study has several limitations. The data do not allow for specific survival analysis because the cause of death is not always coded appropriately. Therefore, only OS was presented. Some coding issues arose with the surgical procedures. For example, transoral laser microsurgery is not specified as an entity. Another reason for the poor representation of transoral laser microsurgery procedures in our cohort could be the fact that the SEER-Medicare database collects data from some centers in some states, which limited us from comparing transoral laser microsurgery directly with other modalities of treatment.

The data set provided limited information about the clinical context in which each salvage laryngectomy was performed. In addition, extrapolation of specific functional assessments of the larynx was difficult. We used tracheostomy and gastrostomy dependence as surrogates for deficient laryngeal function. Finally, the generalizability of our results is limited by the fact that the data set includes only patients older than 65 years.

Conclusions

This study makes us question the current standard of care for treatment of T3 glottic SCC. Our data support the case for continuing to discuss surgery with these patients as their primary treatment for T3 glottic SCC and for maintaining surgical arms in future prospective laryngeal cancer trials that include patients with T3 glottic malignant neoplasms.

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Key Points**Question**

What treatment modality gives the best 5-year overall survival (OS) in T3 glottic squamous cell carcinoma (SCC)?

Findings

In this secondary analysis of data from the SEER and Medicare databases, among 487 patients with T3 glottic SCC, the adjusted hazard ratio for OS was 0.68 for patients receiving surgery alone vs nonsurgical management and 0.75 for patients receiving surgery plus adjuvant treatment vs nonsurgical management.

Meaning

The improved OS in patients with T3 glottic SCC receiving surgery reinforces the need to discuss surgery with all of these patients and to maintain surgical arms in all laryngeal cancer studies.

Figure. Adjusted, Inverse Propensity-Weighted Survival Curves Comparing Overall Survival
CRT indicates chemoradiotherapy;
CT, chemotherapy; and
RT, radiotherapy.

Table 1

Derivation of the Cohort

Step	No. Removed From Previous Step	Total Remaining
Patients with carcinoma of the head and neck within PEDSF	NA	41 680
Glottic primary site	22 100	19 580
Squamous cell histologic finding	688	18 892
T3 tumor stage	17 115	1777
Simultaneous T3 glottic SCC	478	1299
First diagnosis of head and neck cancer	113	1186
Diagnosis after January 1, 1992	20	1166
Medicare Parts A and B coverage without HMO coverage for 12 consecutive mo preceding diagnosis	588	578
66 y and no distant metastasis at diagnosis	91	487

Abbreviations: HMO, health maintenance organization; NA, not applicable; PEDSF, Patient Entitlement and Diagnosis Summary File; SCC, squamous cell carcinoma.

Table 2

Description of the Cohort Stratified by Treatment Modality

Characteristic	No. (%) of Patients ^a			P Value ^b
	CT, RT, or CRT (n = 258)	Surgery Alone (n = 75)	Surgery + RT or CRT (n = 118)	
Age, median (IQR), y	75.0 (11.2)	75.1 (9.9)	73.1 (7.5)	.04 ^c
Follow-up, median, mo	22 (1–178)	39 (0–199)	35 (2–204)	
Sex				
Male	221 (85.7)	NA (>85)	100 (84.7)	.93
Female	37 (14.3)	NA (<15)	18 (15.3)	
Race				
White	212 (82.2)	64 (85.3)	91 (77.1)	.32
Other	46 (17.8)	11 (14.7)	27 (22.9)	
Region				
West	99 (38.4)	22 (29.3)	42 (35.6)	.43
Midwest	47 (18.2)	21 (28.0)	26 (22.0)	
Northeast	49 (19.0)	18 (24.0)	21 (17.8)	
South	63 (24.4)	14 (18.7)	29 (24.6)	
Population density				
Metropolitan	212 (82.2)	62 (82.7)	97 (82.2)	.99
Nonmetropolitan	46 (17.8)	13 (17.3)	21 (17.8)	
Year of diagnosis				
1992–1995	NA (<11)	21 (28.0)	16 (13.6)	<.001
1996–2000	NA (>13)	11 (14.7)	26 (22.0)	
2001–2005	98 (38.0)	24 (32.0)	42 (35.6)	
2006–2009	98 (38.0)	19 (25.3)	34 (28.8)	
Charlson Comorbidity Index ^d				
0	39 (15.1)	NA (<11)	NA (<11)	.42
1	43 (16.7)	NA (<16)	NA (>18)	
2	176 (68.2)	55 (73.3)	84 (71.2)	
Nodal stage				
N0	213 (82.6)	62 (82.7)	86 (73)	.04
N1–N3	NA (<11)	NA (<11)	NA (>16)	
Unknown	NA (<11)	NA (<11)	NA (<11)	

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; IQR, interquartile range; NA, not applicable; RT, radiotherapy.

^aCells with values less than 11 are not shown in accordance with Surveillance, Epidemiology, and End Results–Medicare Data Use Agreement.^bCalculated using the χ^2 test unless indicated otherwise.^cCalculated using the Kruskal-Wallis test.^dScores range from 0 to 2, with greater numbers indicating more comorbidities.

Table 3**Multivariate OS Analyses Comparing Treatment Modalities**

Characteristic	Multivariate Analysis, aHR (95% CI) ^a	P Value ^b
Year of diagnosis: continuous	0.98 (0.95–1.01)	.11
Age: continuous	1.03 (1.02–1.05)	<.001
Sex: male vs female	1.48 (1.04–2.11)	.03
Race: white vs other	1.21 (0.90–1.62)	.22
Marital status: not married vs married	1.25 (0.98–1.59)	.07
Charlson Comorbidity Index ^c		
1 vs 0	1.30 (0.81–2.08)	.28
2 vs 0	2.31 (1.54–3.47)	<.001
Nodal stage: N1–3 vs N0	1.15 (1.03–1.28)	.01
Treatment		
Surgery alone vs CT, RT, or CRT	0.68 (0.49–0.94)	.02
Surgery + RT or CRT vs CT, RT, or CRT	0.75 (0.57–0.98)	.03

Abbreviations: aHR, adjusted HR; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; OS, overall survival; RT, radiotherapy.

^aMultivariate analysis controlled for all variables in the model after weighting by the inverse probability of treatment.

^bCalculated using the multivariable Cox proportional hazards regression model, with significance evaluated based on the Wald test.

^cScores range from 0 to 2, with greater numbers indicating more comorbidities.