The nonsurgical management of early stage (T1/2 N0 M0) laryngeal cancer: A population analysis

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Background. The purpose of this study was to evaluate the patterns of care and survival in the nonsurgical management of early-stage (T1/2 N0 M0) laryngeal cancer.

Study Design. This was a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) database during the period 2004 to 2015. Patients diagnosed with T1/2 N0 M0 laryngeal SCC definitively treated without surgery were included. Study predictors were age, gender, race, marital status, histologic grade, stage, and management strategy defined as radiotherapy (RT), chemotherapy, chemoradiotherapy (CRT), or no treatment. Study outcomes were overall survival (OS) and disease-specific survival (DSS).

Results. In total, 3221 patients comprised the final sample. Over half of the lesions were stage I (63.8%); 74.0%, 24.8%, and 1.2% were located in the glottis, supraglottis, and subglottis, respectively. RT (77.6%) was the preferred nonsurgical treatment modality, followed by CRT (12.7%). A greater proportion of patients with stage II disease (25.1%) received CRT compared with those with stage I (5.6%). Similarly, patients receiving CRT were significantly younger and more likely to present with higher-grade lesions located in the supraglottis and subglottis. In the multivariate model, the risks of both disease-specific and overall death were increased by age, male gender, supraglottic and subglottic location, stage II disease, CRT, and no treatment.

Conclusions. Definitive RT was the preferred treatment modality regardless of tumor characteristics. CRT was more often selectively reserved for younger patients with higher grade, stage II tumors located in the supraglottis and subglottis. This approach may be driven by the poorer rates of survival associated with these particular characteristics. CRT did not appear to improve survival in comparison with RT after controlling for subsite and disease severity; however, future clinical studies are required to validate this finding. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:18−24)

The National Comprehensive Cancer Network guidelines for treating early stage (T1/2 N0 M0) laryngeal cancers currently recommend either surgery or definitive radiotherapy (RT).[1] Surgical options include transoral laser surgery and open partial laryngectomy. Although upfront surgery may provide excellent control and the opportunity for upstaging on the basis of intraoperative findings, early cancers of the oropharynx, hypopharynx, and larynx have demonstrated comparable outcomes with definitive RT.[2-4]

The larynx is divided into supraglottic, glottic, and subglottic subsites. In general, both stage I and II lesions within a given subsite are grouped together and treated as a single entity. Early-stage laryngeal cancers are known to have excellent cure rates with RT alone, and for both stage I and II glottic cancers, disease-specific survival (DSS) rates have been reported to be as high as 80% to 90%.[5,6] For these reasons, many centers prefer to provide initial treatment with definitive RT as a means of preserving laryngeal function. However, even in this favorable population, location and tumor characteristics are known to be associated with increased rates of regional failure and occult disease.[6,7] Compared with stage I lesions, stage II lesions treated with the same RT regimens have demonstrated worse outcomes.[8,9] Furthermore, supraglottic and subglottic locations are known to be negative predictors of survival.[10,11] To date, no large clinical studies have evaluated the added benefit of chemotherapy in these groups of patients with a higher risk.

The purpose of this study was to evaluate the patterns of care and survival in the nonsurgical management of early-stage laryngeal cancer. The primary aim was to report the trends in therapy selection by using a national cancer database. The hypotheses were that patients with nonglottic stage II lesions would receive higher rates of CRT and that the addition of chemotherapy for these patients would be associated with survival improvements over RT alone.

Statement of Clinical Relevance

Nonsurgical therapy is routinely used to manage early-stage laryngeal cancers. Within localized disease, certain tumor characteristics portend higher rates of occult metastases and, therefore, poorer survival. It is presently unclear if this information influences treatment patterns when laryngeal preservation is desired.

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MATERIALS AND METHODS

The data for this study were sourced from the Surveillance, Epidemiology, and End Results (SEER) program database. Institutional review board approval was not required for this study because all patient information has been deidentified and is publicly available upon request.

Patient selection and variables

Between 2004 and 2015, cases were included if the patients had been diagnosed with early-stage (T1/2 N0 M0) primary laryngeal squamous cell carcinoma (SCC). Cases were excluded if the management included surgical resection of the primary tumor. SCC was identified by using the *International Classification of Diseases for Oncology,* 3rd edition (ICD-O-3), morphologic codes 8051/3, 8052/3, 8070/3 - 8076/3, 8083/3, and 8084/3. The location was limited to the larynx with use of the ICD-O-3 topographic codes C32.0 through C32.9 and further subdivided into supraglottic, glottic, and subglottic sites. Predictor variables were age at diagnosis, gender, race, tumor size, tumor grade, American Joint Committee on Cancer (AJCC) stage, and definitive treatment modality. Tumor grade was classified as either low (well differentiated), intermediate (moderately differentiated), or high (poorly differentiated or undifferentiated). AJCC stage was assigned according to the guidelines of the *AJCC Cancer Staging Manual,* 6th edition. Outcome variables were survival years and the cause of death. Overall survival (OS) was defined as the time from diagnosis to death by any cause. DSS was defined as the time from diagnosis to death caused by cancer, according to the SEER guidelines.

Statistical analyses

Descriptive statistics were calculated for all baseline variables. Associations with treatment strategy were identified by using χ^2 tests and analyses of variance (ANOVAs). Kaplan-Meier analyses were used to plot survival and estimate the 1-, 2-, 5-, and 10-year OS and DSS rates. The log-rank test was used to perform univariate survival analyses and test for differences within each predictor variable. All univariate predictors were included in the multivariate model, and time-to-event survival analyses were performed by using Cox proportional hazards regression models. Hazard ratios (HRs) were calculated, and their significance was determined by using the Wald χ^2 test. P value $< .05$ was considered statistically significant, and all analyses were performed with the SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Descriptive statistics

In total, 3221 patients were identified as having early-stage laryngeal cancer that was definitively managed without surgery. The mean age at diagnosis was 66.6 years, and the vast majority of patients were white (83.4%) and males (82.8%) (Table I). In nearly three-quarters of cases, the tumor arose in the glottis (74.0%), followed by the supraglottis (24.8%) and subglottis (1.2%). The distribution of histologic grades was low (24.3%), intermediate (62%), or high (15.6%). The average tumor size was 1.9 cm, and 63.8% of cases had stage I tumors.

The majority of lesions were treated with RT (77.6%), followed by CRT alone (12.7%), no treatment (9.0%), and chemotherapy alone (0.8%). Definitive RT was provided to 84.4% of patients with stage I lesions, but that figure dropped to 65.4% for those with stage II lesions. The treatment choice was significantly associated with age at diagnosis, gender, marital status, subsite, grade, and stage (Table II).

Survival

Of the included patients, 1793 (55.8%) were reported to be alive at their last follow-up. Overall estimated 1-, 2-, 5-, and 10-year survival rates were 89.7%, 81.3%, 62.2%, and 39.8%, respectively. Of the 1422 patients who died, in 491 (34.5%), death was attributable to

Table I. Patient demographic characteristics and tumor characteristics of the entire study sample

	Overall n (%)
Sample size	3221
Age, years†	66.6 ± 11.1
Gender	
Female	554 (17.2)
Male	2667 (82.8)
Race	
White	2676 (83.4)
Black	404 (12.6)
Other	127 (4.0)
Marital status	
Married	1762 (57.7)
Single	481 (15.8)
Divorced/Separated	457 (15.0)
Widowed	353 (11.6)
Subsite	
Supraglottis	764 (24.8)
Glottis	2282 (74.0)
Subglottis	37 (1.2)
Histologic grade	
Low	444 (24.3)
Intermediate	1479 (62.0)
High	372 (15.6)
AJCC stage	
Stage I	2055 (63.8)
Stage II	1166 (36.2)
Size, cm†	1.9 ± 3.8

†Mean ± standard deviation (SD).
AJCC, American Joint Committee on Cancer.

Table II. Patient and tumor characteristics compared among nonsurgical treatment modalities

	Radiation *n (%)*	*Chemotherapy* *n (%)*			
Chemotherapy + Radiation *n (%)*	*No treatment* *n (%)*	*P value*			
Sample size	2498 (77.6)	24 (0.8)	409 (12.7)	290 (9.0)	–
Age, years†	67.0 ± 11.0	67.8 ± 11.2	63.5 ± 10.0	68.0 ± 12.4	< .01*
Gender					< .01*
Female	393 (70.9)	7 (1.3)	94 (17.0)	60 (10.8)	
Male	2105 (78.9)	17 (0.6)	315 (11.8)	230 (8.6)	
Race					.46
White	2087 (78.0)	21 (0.8)	333 (12.4)	235 (8.8)	
Black	297 (73.5)	3 (0.7)	62 (15.4)	42 (10.4)	
Other	102 (80.3)	0 (0)	14 (11.0)	11 (8.7)	
Marital status					< .01*
Married	1399 (79.4)	10 (0.6)	228 (12.9)	125 (7.1)	
Single	348 (72.4)	5 (1.0)	72 (15.0)	56 (11.6)	
Divorced/Separated	364 (79.7)	5 (1.1)	55 (12.0)	33 (7.2)	
Widowed	261 (73.9)	3 (0.9)	36 (10.2)	53 (15.0)	
Subsite					< .01*
Supraglottis	449 (58.8)	10 (1.3)	225 (29.5)	80 (10.5)	
Glottis	1943 (85.1)	9 (0.4)	152 (6.7)	178 (7.8)	
Subglottis	20 (54.1)	3 (8.1)	11 (29.7)	3 (8.1)	
Histologic grade					< .01*
Low	444 (83.3)	2 (0.4)	44 (8.3)	43 (8.1)	
Intermediate	1129 (76.3)	9 (0.6)	215 (14.5)	126 (8.5)	
High	253 (68.0)	9 (2.4)	74 (19.9)	36 (9.7)	
AJCC stage					< .01*
Stage I	1735 (84.4)	9 (0.4)	116 (5.6)	195 (9.5)	
Stage II	763 (65.4)	15 (1.3)	293 (25.1)	95 (8.2)	
Size, cm†	1.7 ± 4.5	2.1 ± 1.2	2.4 ± 1.3	2.0 ± 1.3	.20

*$P < .05$.
†Mean ± standard deviation (SD).
AJCC, American Joint Committee on Cancer.

cancer. Disease-specific 1-, 2-, 5-, and 10-year survival rates were 96%, 92.3%, 84.3%, and 74.5%, respectively.

In the univariate survival analyses, marital status, subsite, stage, and treatment modality were all significant predictors of both OS and DSS (Table III). Age, race, and histologic grade were only associated with OS. Stratifying by AJCC stage, significant differences in OS were found between those receiving CRT and RT for stage I ($P < .01$) but not stage II cancer ($P = .05$) (Figure 1). Patients who received RT had superior survival rates for stage I lesions. The multivariate survival models conducted for both OS and DSS included the predictors age, gender, race, marital status, subsite, grade, stage, and treatment (Table IV). Age 70 years or greater (DSS: HR = 1.41, $P < .01$; OS: HR = 1.95, $P < 0.01$); male gender (DSS: HR = 1.43, $P = .02$; OS: HR = 1.19, $P = .04$); supraglottis (DSS: HR = 1.71, $P < .01$; OS: HR = 1.70, $P < .01$); subglottis (DSS: HR = 2.21, $P = .02$; OS: HR = 1.81, $P = .01$); stage II (DSS: HR = 1.56, $P < .01$; OS: HR = 1.25, $P < .01$); CRT (DSS: HR = 1.65, $P < .01$; OS: HR = 1.35, $P < .01$); and no treatment (DSS: HR = 2.43, $P < .01$; OS: HR = 1.98, $P < .01$) all independently increased the risks of both overall and disease-specific death. Single status (OS: HR = 1.30, $P < .01$); divorced/separated status (OS: HR = 1.37, $P < .01$); widowed status (OS: HR = 1.52, $P < .01$); and chemotherapy (OS: HR = 2.95, $P < .01$) increased the risk of overall death alone.

DISCUSSION

This study sought to evaluate practice patterns with the nonsurgical management of early-stage laryngeal cancer. Although variations exist, definitive RT was predictably found to be the most common treatment choice, regardless of tumor characteristics. CRT was chosen for 25.1% of T2 but only 5.6% of T1 tumors. It is reassuring that nearly all stage I lesions (84.4%) were treated successfully with RT because there is little evidence to support escalating treatment. In fact, it is surprising that any of these patients received CRT, possibly as a result of inaccurate staging of disease. The choice of management was significantly associated with age, gender, marital status, subsite, grade, and stage. Mean age at diagnosis was the lowest for patients who received CRT, and treatment centers may be more willing to add chemotherapy for patients

Table III. Univariate analyses for disease-specific survival (DSS) and overall survival (OS)

	5-year DSS, %	P value*	5-year OS, %	P value*
Age, years		.08		< .01†
< 70	85.2		69.2	
≥ 70	82.8		51.9	
Gender		.51		.20
Female	87.0		60.5	
Male	83.7		62.5	
Race		.10		< .01†
White	84.5		62.7	
Black	81.6		55.7	
Other	83.9		70.5	
Marital status		< .01†		< .01†
Married	85.6		66.5	
Single	79.1		59.7	
Divorced/Separated	84.0		61.0	
Widowed	82.1		43.8	
Subsite		< .01†		< .01†
Supraglottis	76.1		49.3	
Glottis	87.2		67.0	
Subglottis	68.0		39.6	
Histologic grade		.13		< .01†
Low	82.9		62.9	
Intermediate	82.4		60.7	
High	81.3		56.8	
AJCC stage		< .01†		< .01†
Stage I	87.8		66.3	
Stage II	77.9		55.1	
Treatment		< .01†		< .01†
Radiation	87.6		66.6	
Chemotherapy	74.0		20.8	
Chemotherapy + Radiation	71.5		51.0	
No treatment	72.7		42.9	

*By the log-rank test.
†$P < .05$.
AJCC, American Joint Committee on Cancer.

who they believe can tolerate the extra toxicity. There may also be a greater incentive to treat young patients more aggressively. Higher-grade, stage II, and nonglottic location were each associated with CRT. This practice may be driven by the poorer rates of survival associated with these particular characteristics. Nonglottic lesions are often diagnosed late because they are asymptomatic. In addition, the abundant submucosal lymphatics of the supraglottis facilitate early cervical involvement. Similarly, subglottic lesions are thought to behave aggressively with early fibrocartilage invasion as well as paratracheal and mediastinal spread.

A variety of patient, tumor, and treatment characteristics were found to negatively impact survival. In agreement with what is already known for head and neck cancers, older age, male gender, and non-married relationship status were all associated with poorer outcomes. Similarly, nonglottic location and later stage were found to be more prognostic compared with histologic grade. OS with CRT was not superior to that with RT for either stage I or stage II lesions when compared. Patients who received RT for stage I lesions actually experienced better survival compared with those who received CRT. Again, this could stem from questionable staging, rather than true chemotoxicity. Patients receiving RT and CRT for stage II lesions had similar rates of survival. In the multivariate analyses, patients receiving CRT had a greater than 65% increased risk of cancer death and a greater than 35% increased risk of any-cause death compared with patients receiving RT. Similarly, chemotherapy alone and lack of treatment had worse survival results. Given the current tendency to use CRT for treating more advanced tumors, one should be cautious about dismissing the benefits of additional systemic therapy. The differences in survival outcomes between RT and CRT are difficult to interpret, given the confounder disease severity despite attempts to control for grade and stage in the multivariate model.

Concurrent CRT is an acceptable treatment for stage III/IV laryngeal cancers.[1] For locally advanced lesions, CRT is superior to RT alone and offers superior rates of regional control and laryngeal preservation.[12] However, the benefits of chemotherapy added to RT remain unproven for T2 cancers. With RT alone, regional failure rates in early-stage glottic cancers still depend on the size and extent of the primary tumor.[7] The fact that local control is achieved in an estimated 80% to 90% of T1 cancers but only in 65% to 80% of T2 glottic cancers suggests that there may be a role for intensifying treatment in a subset of patients. A retrospective review of records from 10 Japanese institutions found that CRT was performed for 24%, 23%, and 60% of patients with T1 a, T1 b, and T2 glottic cancers, respectively.[13] These rates are substantially greater than what we observed in our U.S. study sample. Adding concurrent chemotherapy for larger T2 glottic lesions has been shown to be both safe and effective for improving laryngeal preservation.[14-17] Compared with RT, concurrent CRT has also been shown to improve DSS for T2 laryngeal cancers presumably by treating occult metastasis.[18] In those studies, treatment with tegafur−uracil, carboplatin, and docetaxel was found to be well-tolerated, without causing major toxicity. However, prospective trials are required to confirm any effect because current evidence is insufficient and mostly anecdotal.[19] Of note, glottic cancers are the focus of nearly all research efforts because of their prevalence. Investigations should also include supraglottic and subglottic cancers, given the differences in their staging and their tendency to present later with occult spread.

This study has several limitations, which have been acknowledged also by previous studies using similar

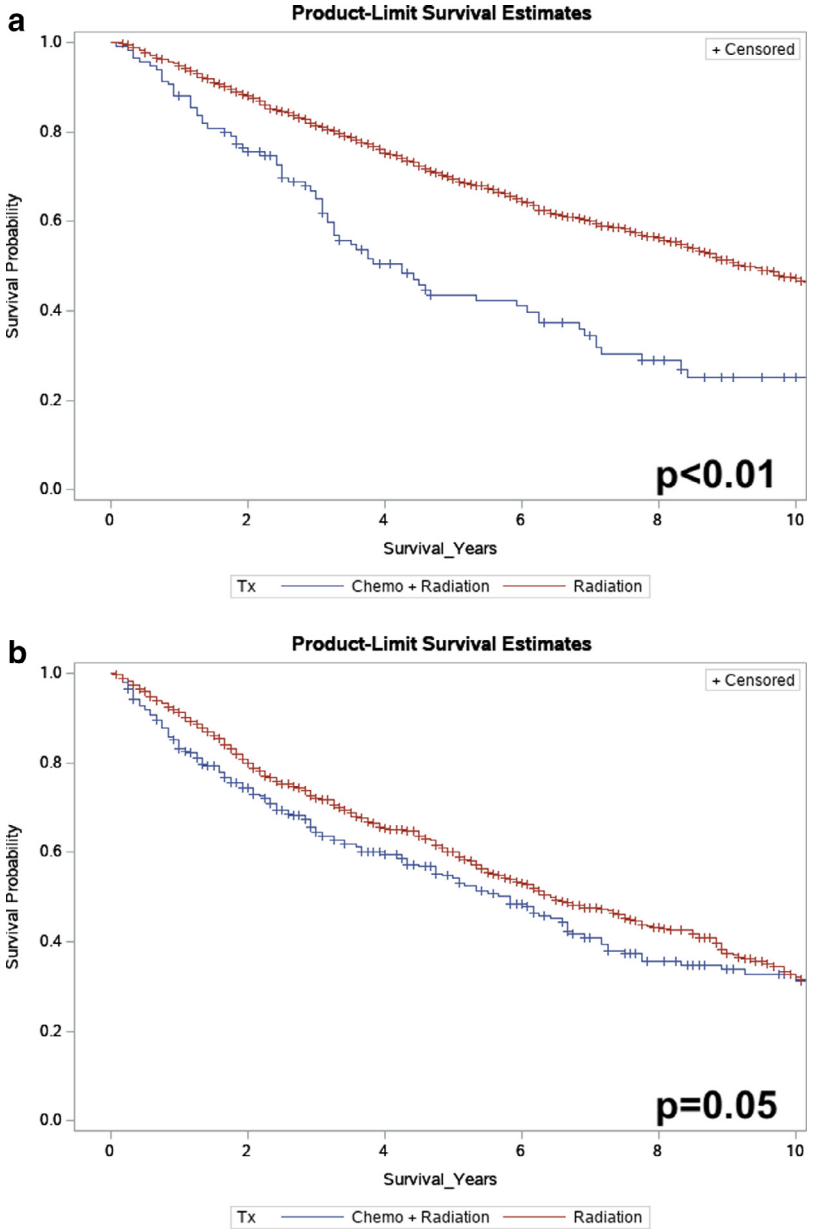

Fig. 1. Comparison of overall survival (OS) between chemoradiotherapy (CRT) and radiotherapy (RT) for stage I **(A)** and stage II **(B)** lesions.

methods . Clinical details were unavailable for some reports, and the coding of patient and tumor characteristics was often vague. The reasons for pursuing nonsurgical management, fractionation schedules, and timing of chemotherapy were not provided in some reports, although treatment decisions were presumably chosen on the basis of the best evidence available. It was also impossible to verify the accuracy and completeness of radiation and chemotherapy data, although this has not precluded their use in previous studies. Treatments received outside of the hospital setting may not have been captured completely, and some patients coded as not receiving either radiation or chemotherapy may have, in fact, received those treatments. In general, outcomes derived from any large administrative database should not be used to make clinical recommendations, and they should, instead, be used to direct future investigation. Still, this analysis was conducted on a representative sample of all U.S. patients with laryngeal cancer, and its results and conclusions are validhelpful for assessing national practice patterns.

CONCLUSIONS

Definitive RT was the preferred management strategy even for high-risk lesions. CRT was more often

Table IV. Cox proportions hazards models for multivariate analyses of disease-specific survival (DSS) and overall survival (OS)

	DSS		*OS*	
	HR (95% CI)	*P value**	*HR (95% CI)*	*P value**
Age, years				
< 70	Ref	–	Ref	–
≥ 70	1.41 (1.13−1.77)	< .01†	1.95 (1.70−2.24)	< .01†
Gender				
Female	Ref	–	Ref	–
Male	1.43 (1.06−1.93)	.02†	1.19 (1.00−1.42)	.04†
Race				
White	Ref	–	Ref	–
Black	0.99 (0.72−1.37)	.97	1.13 (0.94−1.36)	0.20
Other	1.23 (0.76−1.99)	.40	1.00 (0.73−1.39)	.99
Marital status				
Married	Ref	–	Ref	–
Single	1.34 (0.99−1.81)	.06	1.30 (1.07−1.58)	< .01†
Divorced/Separated	1.25 (0.92−1.69)	.15	1.37 (1.14−1.64)	< .01†
Widowed	0.96 (0.63−1.46)	.15	1.52 (1.26−1.85)	< .01†
Subsite				
Glottis	Ref	–	Ref	–
Supraglottis	1.71 (1.33−2.20)	< .01†	1.70 (1.46−1.98)	< .01†
Subglottis	2.21 (1.11−4.39)	.02†	1.81 (1.14−2.89)	.01†
Histologic grade				
Low	Ref	–	Ref	–
Intermediate	0.85 (0.65−1.10)	.22	1.03 (0.87−1.21)	.72
High	0.84 (0.59−1.18)	.31	1.06 (0.86−1.32)	.57
AJCC stage				
Stage I	Ref	–	Ref	–
Stage II	1.56 (1.25−1.95)	< .01†	1.25 (1.09−1.44)	< .01†
Treatment				
Radiation	Ref	–	Ref	–
Chemotherapy	2.23 (0.82−6.10)	.12	2.95 (1.69−5.16)	< .01†
Chemotherapy + Radiation	1.65 (1.24−2.18)	< .01†	1.35 (1.13−1.63)	< .01†
No treatment	2.43 (1.74−3.39)	< .01†	1.98 (1.61−2.44)	< .01†

*By the Wald χ^2 test.
†$P < .05$.
AJCC, American Joint Committee on Cancer; *CI,* confidence interval; *Ref,* reference value.

selectively reserved for younger patients with higher-grade, stage II tumors located in the supraglottis and subglottis. Despite the promising results reported by prior retrospective studies, we did not find CRT to improve survival in comparison with RT for either stage I or II lesions, so future clinical investigations are required to verify this finding. Our finding is contrary to what has been found for locally advanced laryngeal tumors but supports the present National Comprehensive Cancer Network recommendations for single-modality RT for stage II cancers.

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DISCLOSURE

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