Received: 29 September 2019 | Accepted: 21 October 2019

DOI: 10.1002/lio2.327

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Predictors of chemotherapy and its effects in early stage squamous cell carcinoma of the larynx

Thejus T. Jayakrishnan MD[1] | Richard J. White DO[1] | Larisa Greenberg MD[2] | Athanasios Colonias MD[3] | Rodney E. Wegner MD[3]

[1]Department of Internal Medicine, Allegheny Health Network, Pittsburgh, PA

[2]Division of Medical Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA

[3]Division of Radiation Oncology, Allegheny Health Network Cancer Institute, Allegheny General Hospital, Pittsburgh, PA

Correspondence
Rodney Wegner, Division of Radiation Oncology, Allegheny Health Network Cancer Institute, Allegheny General Hospital, Level 02, 320 E. North Avenue, Pittsburgh, PA 15212.
Email: Rodney.wegner@ahn.org

Abstract

Background: Squamous cell carcinoma (SCC) of larynx is a common head and neck cancer. For cases that are node negative, the role of definitive concurrent chemoradiation is unclear and not supported by guidelines but used at provider discretion. To address this knowledge gap, we examined the oncological outcomes with additional chemotherapy and factors correlated with the chemotherapy administration.

Methods: We queried the National Cancer Database for patients with early stage (T2N0M0) laryngeal SCC treated nonsurgically. Multivariable logistic regression identified predictors of chemotherapy. Multivariable Cox regression evaluated predictors of survival. Propensity matching accounted for indication biases.

Results: We identified 7181 patients meeting the eligibility criteria, of which 1568 (22%) patients received chemotherapy in addition to radiation. Predictors of chemotherapy use included younger age, Caucasian race, more remote year of treatment, higher grade, sites other than glottis, treatment at a community cancer center, and use of intensity-modulated radiation therapy. Median overall survival was not significantly different in the two arms analyzed—65 months (95% confidence interval [CI] 60, 72months) with chemotherapy compared to 70 months without chemotherapy (95% CI 66, 75 months, $P<.37$). Predictors for survival on propensity-matched multivariable analysis were increased age, male sex, less education, lower income, higher comorbidity score, receipt of treatment at a community center, and nonglottic sites.

Conclusions: This study shows no clear survival benefit with chemotherapy in early stage disease. Although this implies that chemotherapy should not be routinely delivered, individualized judgment and prospective studies are recommended as the biology behind this interesting finding is undefined.

Level of Evidence: 2C (Outcomes Research).

Prior presentations: Oral presentation at annual meeting of Pennsylvania Society of Hematology and Oncology, Pittsburgh, the United States, September 2019.

KEYWORDS

chemotherapy, glottis, laryngeal cancer, National Cancer Database, subglottis, supraglottis, survival, radiotherapy

1 | INTRODUCTION

Laryngeal cancer is a type of head and neck cancer with an incidence of 3.0 per 100 000 men and women per year. Based on National Cancer Institute data from 2016, there were an estimated 96 351 people living with laryngeal cancer in the United States.[1] In 2019, 12 410 new cases are estimated to be diagnosed and 3760 deaths predicted from this disease.[1] Among the different histological subtypes, squamous cell carcinoma (SCC) accounts for 85%-98% of laryngeal cancers.[2] Although the 5-year overall survival for laryngeal cancer is 61%, the outcome varies by location and stage of the disease as expected.[1] Based on the anatomical location, laryngeal cancers are subdivided into glottis (accounts for 60%), supraglottis (35%), and subglottis (<5%).[1] For laryngeal cancer involving glottis, approximately 80% are diagnosed in the early stages (stage I or II—small primary with no nodal involvement or metastases) with a 5-year survival rate of 90% compared to 44% when diagnosed at an advanced stage (stages III and IV).[1] Compared to this subgroup, patients with cancer involving the supraglottis and subglottis are more likely to be diagnosed in advanced stages due to less symptoms to prompt attention at earlier stages and the presence of abundant lymphatics predisposing to nodal spread.[2,3] The 5-year survival rates are also different—59% (early stage) to 34% (advanced stage) for supraglottic location vs 65% (early stage) to 32% (advanced stage) for subglottic location.[1]

In addition to predicting survival, the stage also guides management of head and neck cancer. Single modality treatment with

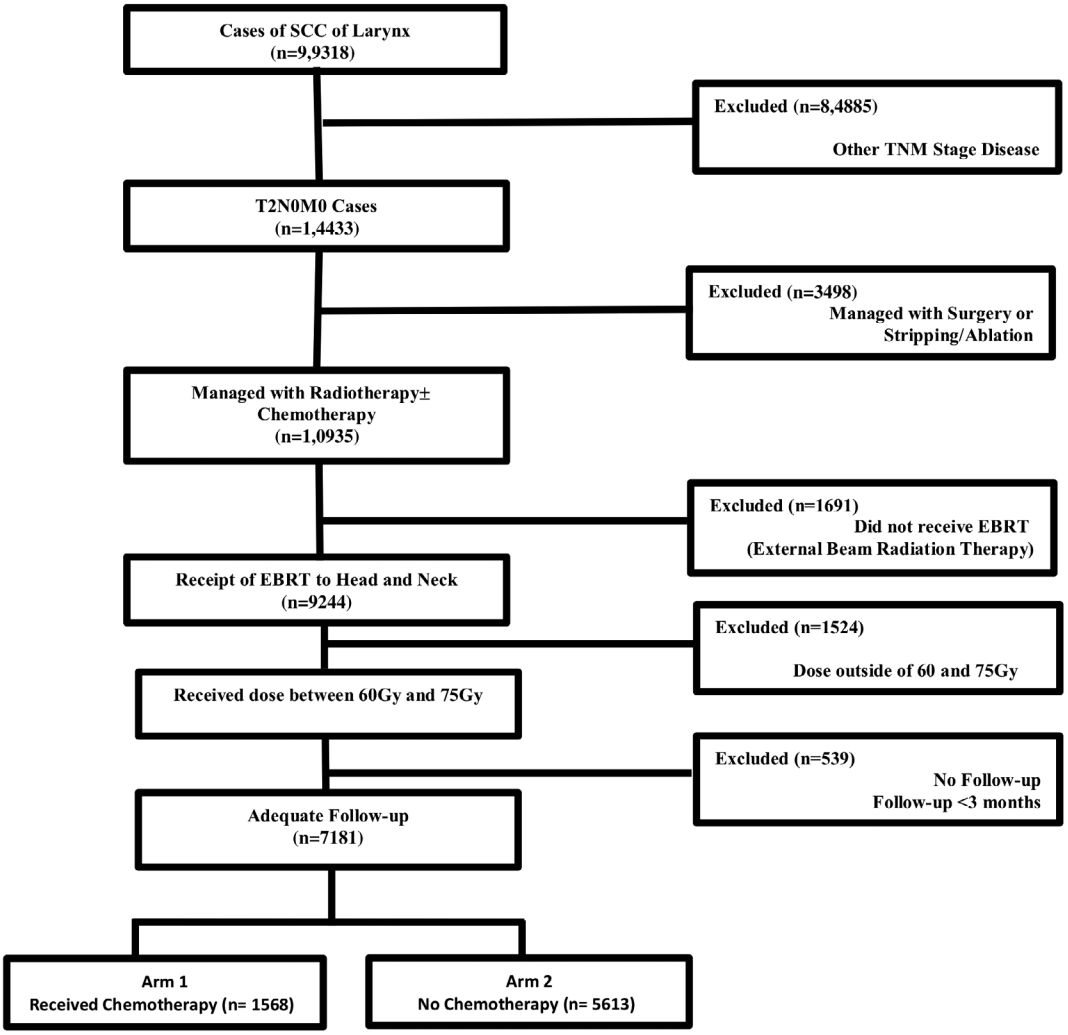


FIGURE 1 Consort diagram outlining the selection criteria for study eligibility

TABLE 1 Baseline characteristics of patients selected for analysis (n=7181)

Characteristics	No. (%)
Age	
≤64	3599 (50.1)
>64	3582 (49.9)
Chemotherapy	
No	5613 (78.1)
Yes	1568 (21.8)
Comorbidity score	
0	5248 (73.1)
1	1370 (19.1)
≥2	563 (7.8)
Distance from facility	
≤9 miles	3532 (49.4)
>9 miles	3613 (50.6)
Facility type	
Community Cancer Center	873 (12.3)
Comprehensive Community Cancer Center	3215 (45.1)
Academic/research program	3037 (42.6)
Site of primary	
Glottis	3689 (51.4)
Supraglottis	2695 (37.5)
Subglottis	137 (1.9)
Laryngeal cartilage	22 (0.3)
Overlapping lesion of larynx	163 (2.3)
Not specified	475 (6.6)
Grade	
Well differentiated	901 (12.6)
Moderately differentiated	3469 (48.3)
Poorly differentiated	1058 (14.7)
Undetermined	1753 (24.4)
Education, % without a high school diploma	
≥29	1819 (25.8)
20-28.9	2209 (31.3)
14-19.9	1848 (26.1)
<14	1187 (16.8)
Median income, USD, by zip code	
<30 000	1865 (26.5)
30 000-34 999	1869 (26.5)
35 000-45 999	1595 (22.7)
≥46 000	1713 (24.3)
Insurance	
None	315 (4.4)
Private	2344 (32.6)
Government	4395 (61.2)
Unknown	127 (1.8)
Location	
Metropolitan	5489 (78.1)
Urban	1315 (18.7)
Rural	224 (3.2)
Race	
Caucasian	6059 (84.4)
African American	961 (13.4)
Other	161 (2.2)
Gender	
Male	5441 (75.8)
Female	1740 (24.2)
Radiation	
3D CRT	4845 (67.5)
IMRT	2336 (32.5)
Year group	
2004-2006	1606 (22.4)
2007-2009	1693 (23.6)
2010-2012	1914 (26.6)
2013-2015	1968 (27.4)

Abbreviation: CI, confidence interval; CRT, chemoradiation therapy; IMRT, intensity-modulated radiation therapy.

radiation therapy (RT) or surgery is recommended for early stage node-negative patients and is determined based on local expertise and multidisciplinary discussion.[3] Comorbidites and quality of life are also important considerations in choosing the appropriate therapy.[3] We hypothesized that concurrent chemoradiation continues to be used in the management of early stage laryngeal cancer despite the guidelines and sought to explore the predictors and impact on the oncological outcome.

2 | METHODS

The methods for performing an analysis of the National Cancer Database (NCDB) have been described previously.[4,5] We conducted a retrospective review using de-identified data from the NCDB; therefore the study was exempt from Institutional Review Board oversight. Jointly maintained by the American Cancer Society and the American College of Surgeons, the NCDB encompasses approximately 70% of newly diagnosed malignancies each year across the United States. We queried the NCDB for patients diagnosed between 2004 and 2015 with SCC of larynx. We excluded patients with TNM stages other than T2N0M0, those treated with surgery, stripping or ablation, and those who did not receive external beam RT (EBRT) in the dose range of 60-75 Gy. Patients with less than 3 month follow-up were excluded to account for immortal time bias. Figure 1 outlines the patient selection process. These patients (age range: 18-90) were particularly chosen for as they are those that received the currently

TABLE 2 Multivariate logistic regression for likelihood of receiving chemotherapy

Characteristics	Odds ratio (95% confidence interval)	*P* value
Age		
≤64	Reference	
>64	0.66 (0.57-0.76)	<.0001
Gender		
Male	Reference	
Female	0.93 (0.81-1.07)	.2941
Comorbidity score		
0	Reference	
1	1.18 (1.02-1.37)	.0287
≥2	0.91 (0.72-1.14)	.3939
Distance to facility		
≤9 miles	Reference	
>9 miles	1.13 (0.99-1.29)	.0738
Facility type		
Community Cancer Center	Reference	
Comprehensive Community Cancer Center	0.76 (0.63-0.91)	.0038
Academic/research program	0.83 (0.68-0.99)	.0496
Grade		
Well differentiated	Reference	
Moderately differentiated	1.31 (1.07-1.61)	.0096
Poorly differentiated	1.73 (1.37-2.18)	<.0001
Site of primary		
Glottis	Reference	
Supraglottis	3.19 (2.78-3.67)	<.0001
Subglottis	2.04 (1.35-3.09)	.0007
Laryngeal cartilage	2.54 (0.01-6.39)	.0482
Overlapping lesion of larynx	2.15 (0.47-3.15)	.0001
Not specified	2.95 (0.35-3.71)	<.0001
Radiation technique		
3D CRT	Reference	
IMRT	1.69 (1.48-1.93)	<.0001
Education, % without high school diploma		
≥29	Reference	
20-28.9	0.94 (0.79-1.11)	.4617
14-19.9	1.01 (0.83-1.24)	.8797
<14%	0.94 (0.73-1.20)	.6123
Median income, USD		
<30 000	Reference	
30 000-34 999	1.04 (0.87-1.25)	.6498
35 000-45 999	1.10 (0.90-1.35)	.3596
≥46 000	1.04 (0.82-1.32)	.7522
Insurance		
None	Reference	
Private	0.82 (0.62-1.08)	.1665
Government	0.95 (0.71-1.26)	.7084
Location		
Metropolitan	Reference	
Urban	0.94 (0.79-0.1.11)	.4555
Rural	0.93 (0.65-1.32)	.6707
Race		
Caucasian	Reference	
African American	1.18 (0.98-1.42)	.0769
Other	0.54 (0.32-0.88)	.0144
Gender		
Male	Reference	
Female	0.93 (0.81-1.07)	.2941
Year		
2004-2006	Reference	
2007-2009	1.03 (0.86-1.22)	.7710
2010-2012	0.84 (0.70-0.99)	.0422
2013-2015	0.59 (0.49-0.71)	<.0001

Abbreviations: CI, confidence interval; CRT, chemoradiation therapy; IMRT, intensity-modulated radiation therapy.

recommended and maximum therapy allowing them the highest potential benefit from treatment. The resultant patient group was then split into those with chemotherapy incorporated into their treatment regimen concurrent with radiation and those not. Time to chemotherapy and radiation was calculated to confirm that they mirrored each other in the setting of concurrent treatment.

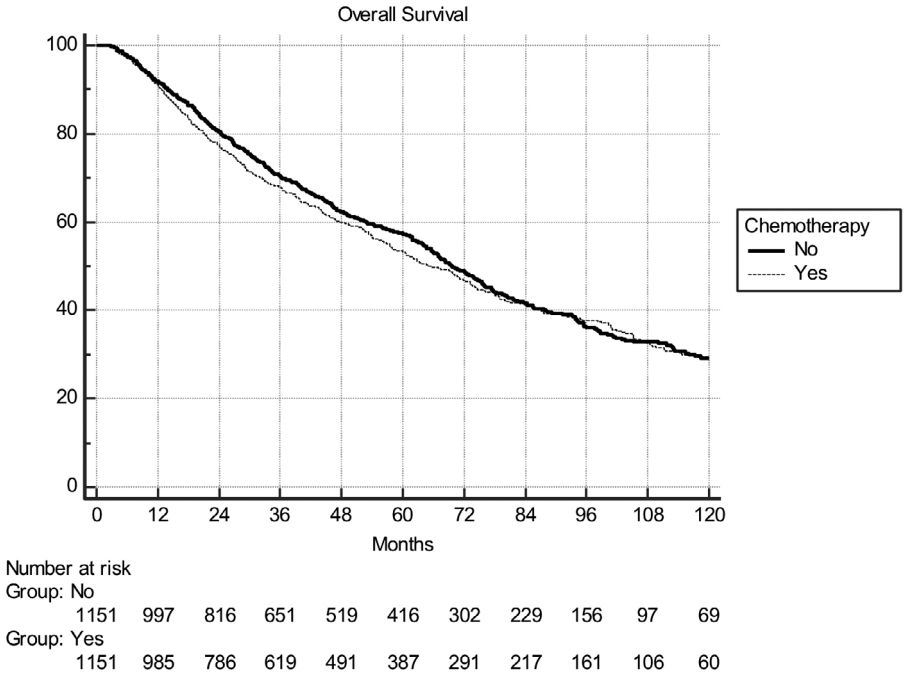
Race was divided into three broad categories including Caucasian, African American, or other. Comorbidity was quantified using the widely accepted and verified Charlson/Deyo comorbidity index.[6] Socioeconomic data in the patients' residence census tract were provided as quartiles of the percentage of persons with less than a high school education and median household income. The facility type was assigned according to the Commission on Cancer accreditation category. Locations were assigned based on data provided by the U.S. Department of Agriculture Economic Research Service. Insurance status is documented in the NCDB as it appears on the admission page. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Data were analyzed using Medcalc Version 18 (Ostend, Belgium). Summary statistics are presented for discrete variables. Chi-squared testing compared patient, treatment, and disease-related characteristics between the two treatment groups. Overall survival was calculated in months from time of diagnosis to date of last contact or death as is standard within the NCDB. Kaplan-Meier curves were used to

FIGURE 2 Results of propensity matched survival analysis represented using Kaplan-Meier curve

Mean and median survival

Factor	Median	95% CI for the median
No chemo	69.550	65.910 -75.070
Chemo	65.350	60.190 -72.310



calculate cumulative probability of survival.[7] Log-rank statistics were used to test for significant differences in the cumulative proportions across groups. A Cox proportional hazards model was used for multivariable survival analysis.[8] Due to the large nature of the data set, factors significant on univariable Cox regression were entered using a stepwise backward elimination process. Adjusted hazard ratios and 95% confidence intervals (CI) are reported, using an alpha level of .05 to indicate statistical significance.

Propensity score-adjusted survival analysis was used to account for indication bias due to lack of randomization between patients receiving and not receiving chemotherapy.[9] Multivariable logistic regression was used to calculate a propensity score indicative of the conditional probability regarding receipt of chemotherapy. The propensity model included observable variables associated with treatment selection on multivariable logistic regression. A Cox proportional hazards model was then constructed incorporating the propensity score.

3 | RESULTS

The data set included 99 318 eligible patients, of which 7181 patients with early stage (T2N0M0) laryngeal SCC were identified after exclusion (Figure 1). Of these, 1568 (22%) patients received chemotherapy as part of their treatment after RT. Table 1 displays patient characteristics associated with the entire cohort. The median age was 64 (range: 19-90) years. The median time to start of treatment (radiation alone or chemoradiation) after diagnosis was 34 (range: 26-48) days. The median radiation dose was 70 Gy (range: 60-74) in 35 fractions (range: 32-35).

On multivariable logistic regression predictors of chemotherapy use included younger age, Caucasian race, earlier year of treatment, higher grade, sites other than glottis, treatment at a community cancer center, and use of intensity-modulated RT (IMRT) (Table 2). Comorbidity scores 2 and 3 are grouped together as the number of patients with score 3 were very low (n = 560).

The median follow-up for the entire group was 39 months (range: 2-163 months). Median overall survival was 68 months for all patients (95% CI 65-72 months). The median overall survival was 65 months (95% CI 60-72 months) with chemotherapy compared to 70 months without chemotherapy (95% CI 66-75 months, $P < .37$) (Figure 2). The 3-year overall survival was 68% (95% CI 66%-70%) with chemotherapy vs 70% (95% CI 68%-72%).

Variables that were statistically significant in predicting for death were identified using multivariate analysis and as described in Section 2, a logistic regression then was used to generate a propensity score. The logistic regression model included age, gender, facility type, education level, insurance type, location, race, and year group as they were the significant predictors. Multivariable analysis with propensity score included was then run to determine predictors of outcome (excluding those factors used to generate propensity score). On propensity-matched analysis, overall survival was 65 months (95% CI

TABLE 3 Propensity matched multivariate Cox regression analysis for overall survival

Characteristics	Hazards ratio (95% CI)	*P* value
Age		
≥64	Reference	
>64	1.58 (1.47-1.71)	<.0001
Gender		
Male	Reference	
Female	0.88 (0.81-0.96)	.0029
Chemotherapy		
No	Reference	
Yes	1.08 (0.99-1.17)	.06
Comorbidity score		
0	Reference	
1	1.24 (1.14-1.35)	<.0001
≥2	1.54 (1.37-1.73)	<.0001
Facility type		
Community Cancer Center	Reference	
Comprehensive Community Cancer Center	0.93 (0.84-1.04)	.2194
Academic/research program	0.90 (0.84-0.96)	.0021
Site of primary		
Glottis	Reference	
Supraglottis	1.34 (1.25-1.44)	<.0001
Subglottis	1.26 (0.99- 1.60)	.0600
Laryngeal cartilage	1.81 (1.07-3.06)	.0277
Overlapping lesion of larynx	1.18 (0.94-1.47)	.15
Not specified	1.12 (0.97-1.29)	.11
Education, % without high school diploma		
≥29	Reference	
20-28.9	0.97 (0.88-1.07)	.55
14-19.9	1.09 (1.01-1.18)	.0353
<14%	1.01 (0.87-1.16)	.92
Income, USD		
<30 000	Reference	
30 000-34 999	0.97 (0.88-1.08)	.63
35 000-45 999	0.89 (0.81-0.97)	.0076
≥46 000	0.90 (0.82-0.98)	.0123
Insurance		
None	Reference	
Private	1.15 (0.95-1.39)	.16
Government	0.71 (0.65-0.77)	<.0001
Race		
Caucasian	Reference	
African American	1.06 (0.93-1.16)	.4681
Other	0.74 (0.57-0.96)	.0234

Abbreviation: CI, confidence interval.

60-72 months) vs 70 months (95% CI 66-75 months) in patients receiving and not receiving chemotherapy, respectively (*P* = .37). Increased age, male sex, less education, lower income, Caucasian race, higher comorbidity score, lower education, private insurance, receipt of treatment outside at a community center, supraglottis location, or involvement of laryngeal cartilage predicted for poorer overall survival on propensity-matched multivariable analysis as shown in Table 3.

4 | DISCUSSION

Laryngeal cancer, along with cancers involving the oral cavity and pharynx, accounts for 3.7% of the new cancer cases in the United States.[10] Risk factors for these cancers include smoking and alcohol use which also predispose this population to secondary malignancies involving other parts of the aerodigestive tract exposed to the carcinogens.[11] Studies have also shown a causal association of Human Papilloma virus (HPV) infection with squamous cell carcinoma of the head and neck.[11] Appropriate staging is a crucial part of laryngeal cancer treatment due to its role in prognostication as well as in guiding treatment.[3] Small primary tumor without nodal involvement or metastases is considered early stage laryngeal cancer whereas larger disease with local invasion or metastases represents advanced disease. For early stage laryngeal cancer, there has been mixed results when comparing RT with surgery. Although at least two studies demonstrated equivalent outcomes (5-year overall survival (OS) 75%-77%),[12,13] others have failed to reproduce these results and showed better outcomes in terms of overall survival and larynx preservation for patients treated with larynx preserving surgery compared to RT.[14] Therefore, the therapy is chosen based on anticipated functional outcomes, patient wishes, reliability in terms of patient follow-up, their general medical condition and determined based on multidisciplinary discussion.[15]

The results of the present study confirm that chemotherapy is still delivered with RT in a significant number (22%) of patients with T2N0 laryngeal cancer, despite recommendations from national guidelines advocating for definitive radiation alone.[3] Granted, our data set lacks complete clinical data so there are likely other confounding factors which sway practitioners to delivery chemotherapy. For example, nonglottis sites such as the supraglottis will be richer in lymphatics and have higher risk of nodal involvement, perhaps influencing treatment decisions on systemic therapy.[3] In support of that notion, our analysis showed increased use of chemotherapy when IMRT was used. One could postulate that IMRT was likely used to treat the nodal areas at risk, and perhaps other factors were also present indicating more aggressive disease (ie bulky tumors, impaired cord mobility).

Other predictors for receipt of chemotherapy included Caucasian race, younger age, less comorbidity, presence of moderately differentiated or poorly differentiated cancer, more remote year of treatment, and treatment at a community cancer center. The higher prevalence of chemotherapy among Caucasian patients may just reflect the ongoing racial bias in cancer treatment that is well established.[16-19] As treatment incorporates patient's comorbidities and willingness to tolerate toxicity, it could be assumed that younger age and patients with

less comorbidities received aggressive care including the incorporation of chemotherapy with better outcome in mind. This has been reflected in other studies as well.[19-21] Likewise, patients with moderately to poorly differentiated cancer may have received chemotherapy with hopes for better results. Oncologist's personal bias from clinical experience could have contributed to the use of chemotherapy in these cases despite the fact that the disease was staged as node negative and not recommended by guidelines.[22] Increased receipt of chemotherapy in patients treated at community centers may reflect the difference in practice patterns and adherence to guidelines between community centers and academic or research institutions.[19] It is reassuring that when stratified by time periods, patients studied from more recent years (2010-2015) were less likely to receive chemotherapy showing that the practice patterns may in fact have changed over time as demonstrated previously by others.[19]

Lastly, it may not be overlooked that the results may simply represent extrapolation of recommendations for advanced stages of laryngeal cancer based on patient or physician preference. For patients with advanced staged cancer, if total laryngectomy is indicated and laryngeal preservation is desired, results of intergroup trial RTOG 91-11 supports the use concurrent systemic therapy and RT.[15,23] The trial showed a statistically significant higher rate for laryngeal preservation (88%) at 2 years with concurrent RT with chemotherapy (Cisplatin) compared to induction chemotherapy (74%) and RT alone treatments (69%). The survival outcomes were similar in these groups. Long-term follow-up (10 years) continued to demonstrate superiority of the concurrent cisplatin/RT compared to other modalities.[23] Induction chemotherapy is considered an option in patients who require total laryngectomy but not for early stage cancers.[23] Patients with locally advanced disease (T4) are also recommended adjuvant treatment (RT or systemic therapy/RT) following total laryngectomy with thyroidectomy and neck dissection.[24]

As is clear from the preceding section, RT is a key aspect of management of this cancer type. The dose varies from 66 to 70 Gy using the conventional definitive fractionation techniques.[3] Among the various techniques for delivering RT, IMRT where the intensity of radiation is precisely modulated to decrease doses to normal tissues has emerged as the predominant modality for treatment.[25,26]

The median overall survival for early stage (T2N0) SCC of larynx based on our study was 68 months (95% CI 65-72 months) which is consistent with other studies.[2,12,13] The finding that survival outcomes did not differ between the chemotherapy and nonchemotherapy groups supports the existing NCCN recommendations.[3] Use of chemoradiation therapy can result in complications such as renal failure and bone marrow suppression.[19] Later complications, such as persistent dysphagia, gastrostomy tube dependency, pharyngoesophageal stenosis, chronic lung aspiration, and permanent tracheotomy dependence, have also been found to occur diminishing the benefit of this approach in advanced laryngeal cancer.[27] With regard to other factors affecting survival, the negative relation of age with survival in the present cohort has been previously demonstrated, whereas the association of other sociodemographic variables and tumor characteristics need to be explored further in future studies.[2]

As is typical with these types of analyses, this study was limited by the data provided in the NCDB due to its retrospective nature and inherent selection bias. Chemotherapy delivery is associated with costs and complications. The lack of this data as well as information on toxicity, local failure, details of systemic therapeutic agent(s) used remains a limitation of this study as all of this play an important role in management and ultimately outcome. It is also possible that chemotherapy was utilized in conjunction with RT to improve local control although avoiding salvage laryngectomy.[28-32]

To conclude, the present study shows no clear survival benefit with chemotherapy in early stage disease. Although this implies that chemotherapy should not be routinely delivered, individualized judgment is still recommended and prospective studies are recommended as the biology behind this interesting finding is unclear.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval

Study was conducted using deidentified data from National Cancer Database and was exempt from Institution Review Board Oversight.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Thejus T. Jayakrishnan https://orcid.org/0000-0002-3636-0353
Richard J. White https://orcid.org/0000-0002-7891-721X

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How to cite this article: Jayakrishnan TT, White RJ, Greenberg L, Colonias A, Wegner RE. Predictors of chemotherapy and its effects in early stage squamous cell carcinoma of the larynx. *Laryngoscope Investigative Otolaryngology*. 2020;5:445–452. https://doi.org/10.1002/lio2.327