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Survival Outcomes in Patients with T2N0M0 (Stage II) Squamous Cell Carcinoma of the Larynx

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Abstract

Objective—Emerging data have demonstrated suboptimal outcomes among patients with stage II larynx cancer. Our objective is to report survival outcomes for T2N0M0 larynx cancer, and to determine the cause-specific survival.

Study Design—Case series with planned data collection.

Setting—Tertiary academic center.

Subjects—Adults with T2N0M0 squamous cell carcinoma of the larynx treated with curative intent.

Methods—A head and neck cancer epidemiology database was queried for eligible subjects from 2003-2014. Data were extracted from the electronic medical record and research database and survival analyses were performed.

Results—Thirty-four patients with previously-untreated stage II larynx cancer were identified (median follow-up 48 months). Patients included 27 males and 7 females with a mean age of 59 years. The majority of tumors arose from the glottis (59%). Of the cohort, 12% were treated with surgery, 65% radiation therapy, and 24% chemoradiation therapy. The estimated two-year overall survival was 81%, (95% CI, 59%-92%), disease-specific survival was 91%, (95% CI, 69%-98%), and recurrence-free survival was 84%, (95% CI, 65%-93%). Four out of 5 patients with persistent

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or recurrent disease post-treatment were successfully salvaged with total laryngectomy with 100% locoregional control. There were 11 mortalities (two disease related, two due to metachronous primaries, three treatment related, and four from other/unknown causes).

Conclusion—Stage II laryngeal cancer has suboptimal survival outcomes. This appears to be a reflection of medical comorbidities, propensity for metachronous primaries, and the sequelae of late treatment effects rather than poor locoregional control.

Keywords

Laryngeal tumors; stage II laryngeal cancer; laryngeal malignancy; neoplasm; squamous cell carcinoma; early stage larynx cancer

Introduction

Early stage squamous cell carcinoma (SCC) of the larynx has historically favorable outcomes with single-modality therapy. Traditionally, T1N0M0 (stage I) and T2N0M0 (stage II) tumors have been treated with either definitive radiation therapy or endoscopic microlaryngeal surgery, with no significant differences observed in locoregional control rates between treatment modalities.¹⁻⁴ Both regimens allow for the possibility of salvage options in the event of locoregional failure. As a result, much of the debate regarding optimal treatment of early stage laryngeal cancers has focused on laryngeal preservation and functional outcomes including quality of voice and swallowing function.

For tumors arising from the glottic subsite, the 5-year disease specific survival (DSS) for stage I patients is reportedly 94 – 99% with equally excellent laryngeal preservation rates of approximately 95%.^{5,6} However, these percentages drop precipitously for stage II glottic tumors, with 5-year DSS ranging from 79 - 95% and laryngeal preservation rates of 76 - 82%.⁵⁻⁷ As a result of unexpectedly worse outcomes observed in T2 tumors, the traditional wisdom of treating these two stages with the same management algorithm has been challenged.^{8,9} Alternatively, others have offered explanations for the disparate outcomes in T2 tumors such as understaging or factors including metachronous primaries or medical comorbidities.^{2,7,9}

Herein, we report our experience treating stage II laryngeal SCC in order to identify patient characteristics, treatment modalities, or other associated factors contributing to survival outcomes observed in this group.

Materials and Methods

We performed a retrospective case series analysis by querying a single-institution database with planned data collection of patients with head and neck cancer. The University of Michigan Medical School IRB approved the protocol for which all patients gave informed consent. We included patients 18 years or older with previously untreated T2N0M0 (stage II) laryngeal SCC diagnosed between February 2003 and June 2014 at the University of Michigan in the Department of Otolaryngology – Head and Neck Surgery. Demographics, treatment modality, recurrence pattern, and outcomes were collected. Patients were staged in

accordance to the 7th edition American Joint Committee on Cancer (AJCC) Staging System.¹⁰ Accurate staging was confirmed by rigorous review of clinical, radiographic, and pathologic data (a number of patients initially classified as T2 were upstaged to T3 based upon paraglottic space involvement, and were thus excluded). Smoking status was defined as current (smoked within the prior year), former (cessation of tobacco use more than 12 months prior to diagnosis), and never smokers. Functional laryngeal preservation required an intact larynx without a percutaneous gastrostomy tube or tracheostomy at the time of follow-up.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc) for Windows. Analyses were completed in June 2016. Overall survival was calculated from the date of diagnosis to death or last follow-up. Disease-specific survival was calculated from the date of diagnosis to death or last or last follow-up. An event was defined as a death secondary to the index cancer. Recurrence-Free survival was calculated from the date of diagnosis to date of first recurrence or last follow-up. Patients who died from causes other than the index malignancy were censored at the date of death for DSS and RFS calculations. The Kaplan-Meier method was used to calculate OS and DSS with 95% confidence intervals (CI) of the point estimates using the life table method.

Results

Demographics

There were 34 patients were identified with T2N0M0 (stage II) laryngeal SCC diagnosed between 2003 and 2014 with a median follow-up of 48 months (Table 1). The mean age of patients was 59 years and the male/female ratio was 3.86/1. The majority of patients were either current (61%, 20/34) or former (33%, 11/34) smokers. The majority of tumors arose from the glottis (59%, 20/34) followed by the supraglottis (41%, 14/34). Most patients were treated with single modality therapy including either radiation therapy (65%, 22/34) or surgery alone (12%, 4/34). Of the patients treated with surgery alone, patients underwent endoscopic laser-assisted resections including endoscopic vertical partial laryngectomy (50%, 2/4) or endoscopic supraglottic laryngectomy (50%, 2/4). However, 24% of patients underwent concurrent chemoradiation therapy due to presence of high risk features (bulky primary tumor, impaired vocal fold mobility, infiltrative clinical appearance) based upon the clinical judgment of the institutional multidisciplinary tumor board.

Survival outcome

The estimated 2-year OS was 81%, (95% CI, 59% - 92%), and 2-year DSS was 91%, (95% CI, 69% - 98%) (Figure 1A and 1B). The 2-year recurrence-free survival (RFS) was 84%, (95% CI, 65% - 93%) (Figure 1C). The 5-year DSS and RFS remained at 91% (95% CI, 69 - 98%), and 84% (95% CI, 65% - 93%), respectively.

Recurrence and mortality patterns

Locoregional control was achieved in 85% (29/34) of cases with mean time to relapse or evidence of treatment failure/persistent disease of 6 months (ranging from 1 to 19 months) (Table 1). The patients with locoregional recurrence had tumors arising from the supraglottis

60% (3/5) and from the glottis 40% (2/5) of the time and were treated primarily with radiation therapy (4/5) or chemoradiation therapy (1/5). Four out of 5 patients with persistent or recurrent disease post-treatment were successfully salvaged with total laryngectomy with 100% (4/4) locoregional control. One patient was found to have unresectable carotid involvement intraoperatively (Figure 2). The overall organ preservation rate was 83% (28/34). Four of the five patients who did not achieve functional or oncologic laryngeal preservation were successfully treated with a total laryngectomy (Table 1).

Of the cases of locoregional recurrence, one was alive with no evidence of disease (ANED), two died of other causes (DOC), and two died of disease (DOD) at the time of follow-up (Figure 2). These were the two disease related mortalities in our cohort; one due to loss of locoregional control and one from distant metastasis. Of the remaining 9 mortalities observed in this case series, 3 died of treatment related complications (malnutrition with percutaneous gastrostomy tube complication, respiratory arrest secondary to aspiration event, and epidural abscess likely seeded after pharyngeal dilation), 2 due to metachronous primaries (lung cancer), 1 of natural cause, and 3 of unknown causes (Figure 3).

Discussion

Patients with stage II laryngeal SCC have overall survival outcomes mirroring patients with advanced stage disease despite a treatment paradigm that considers them to have “early stage” disease.¹¹ In our experience treating stage II laryngeal SCC at a tertiary academic center, we found a 2 and 5-year DSS of 91% and functional laryngeal preservation rate of 83%, consistent with previously published reports.⁵⁻⁷ However, current Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancer recommend no difference in the management of early stage (I vs. II) laryngeal malignancies.¹² This trend has led clinicians and researchers to question the contemporary treatment paradigm and determine prognostic indicators that might suggest a rationale for improving outcomes. To date, no consensus explanation or strategy has been published, although it is logical to consider treatment escalation with combined chemotherapy and radiation for patients with advanced, deeply infiltrative T2 lesions.

One potential explanation for inferior outcomes in T2 laryngeal tumors is the difficulty in distinguishing between T2 and T3 tumors clinically, resulting in understaging and ultimately under-treatment. This is especially true with regard to the difficulty in determining thyroid cartilage and/or paraglottic space involvement on cross-sectional imaging in early-to-mid stage laryngeal tumors.¹³ However, we rigorously reviewed the staging of our cohort to avoid the inadvertent additions of T3 tumors that may have skewed the results of prior large database studies that lack the ability to review individual patient records. Thus, these data support the notion that stage II laryngeal cancers have a demonstrably worse outcome compared to stage I cancers despite accurate staging.

Quality data comparing surgery versus radiation for stage II laryngeal cancer are lacking and consist primarily of retrospective, single-institution studies that combine both stage I and II tumors.^{1,2,14-16} The overall results of these studies have been equivocal in terms of survival and functional voice outcomes.¹⁷ Likewise, the small size of our cohort of patients treated

with a variety of regimens obviates meaningful comparisons of outcomes based upon treatment modality in stage II laryngeal cancer. Our data reflect our group's preference for non-surgical therapy in the majority of T2 laryngeal lesions. However, our excellent observed outcomes in the small subset of selected patients treated surgically represents the real-life complexities of treating the heterogeneous tumors that make up this group, and the challenge inherent to any broad conclusions regarding optimal treatment on a population level.¹⁸

Our group did escalate the treatment of selected stage II patients to include concurrent chemoradiation therapy.^{19,20} While such treatment is not supported by current NCCN guidelines, and randomized evidence is lacking to document improved OS or DSS, concurrent chemoradiation therapy in locally advanced laryngeal cancer has shown improved rates of locoregional control and larynx preservation in selected circumstances, and thus framed our decisions.¹⁹⁻²¹ Given these findings, and the potential added toxicity of combined therapy, we would caution the suggestion of escalating therapy in stage II tumors based upon T stage alone.

In our series, the majority of deaths were due to factors other than the index malignancy including treatment-related complications, metachronous primaries, or unrelated/unknown causes. In 1990, Howel-Burke *et al* made a similar observation in their series of 114 patients of T2 glottic cancers in which only 7 died of disease. The remaining mortalities were also secondary to associated comorbidities and metachronous primaries. Multiple studies have cited a high rate of metachronous primaries in patients treated for early glottic cancer ranging from 22 – 30%, with overall survival estimates lower at 5 years among these patients.^{22,23} Cancer survivorship involves a host of complex physical and social sequelae which, as a field, we have not yet fully described.²⁴ The chronic complications associated with prior treatment was also addressed in the long-term results of the RTOG 91-11 trial which showed an increase in late deaths unrelated to the primary malignancy in patients treated with concomitant therapy, suggesting the idea that many “censored” mortalities may in fact be due to treatment-related events.²¹ Ward *et al* further investigated this theory and found that severe late dysphagia was not contributing to these mortalities, but medical comorbidities are a fundamental component of survivorship care.²⁵ The findings of our study suggest that the outcomes in this group are likely explained by a combination of complex inter-related factors that are patient-specific, rather than related to the primary tumor itself.

Our study has several limitations, the size of the cohort being foremost. Given our small cohort, the three patients with unknown causes of death could have a significant impact on our results. In addition, sample size obviates robust subgroup analyses based upon tumor location, smoking status, or treatment modality. Also, our analysis combined glottic and supraglottic tumors which could have altered the results given the reportedly worse outcomes observed in supraglottic tumors.⁶ Finally, the use of a retrospective cohort introduces inherent bias into the analysis. Follow-up studies are clearly warranted. Nevertheless, this is a robust case series of stage II laryngeal SCC employing a database with planned data collection, and as a result the tumor staging of this cohort is likely more

accurate than that of large databases such as SEER, adding credence to the observations of population-based data.

Conclusion

Stage II laryngeal cancer has suboptimal survival outcomes. This appears to be a reflection of medical comorbidities, propensity for metachronous primaries, and the sequelae of late treatment effects rather than poor locoregional control of the incident malignancy. Proactive prevention and management of competing mortalities and treatment sequelae rather than escalation of cancer treatment appear warranted in order to improve outcomes for this patient cohort.

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Figure 1.

A. Overall survival (OS) in patients with stage II laryngeal squamous cell carcinoma.

B. Disease specific survival (DSS) in patients with stage II laryngeal squamous cell carcinoma.

C. Recurrence-free survival (RFS) in patients with stage II laryngeal squamous cell carcinoma.

Abbreviations: KM = Kaplan Meier

Figure 2.

Treatment algorithm in cases with locoregional recurrence.

Abbreviations: ANED = alive with no evidence of disease; DOC = died of other cause; DOD = died of disease

Figure 3. All-cause mortality in T2N0MO of laryngeal squamous cell carcinoma

Table 1
Descriptives: T2N0M0 Squamous Cell Carcinoma of the Larynx

Characteristic	Totals
<i>Number of Subjects</i>	N = 34
<i>Demographics</i>	
Age in years, mean (range)	59 (33 – 80)
Sex, male/female (ratio)	27/7 (3.86:1)
<i>Smoking status, No. (%)</i>	
Current	20 (61)
Former	11 (33)
Never	2 (6)
<i>Anatomic site, No. (%)</i>	
Glottis	20 (59)
Supraglottis	14 (41)
<i>Treatment, No. (%)</i>	
Radiation therapy	22 (65)
Chemoradiation therapy	8 (24)
Surgery	4 (12)
<i>Locoregional relapse or persistent disease, No. (%)</i>	
No	29 (85.3)
Yes	5 (14.7)
<i>Larynx preservation, No. (%)</i>	
Yes	28 (82.4)
No	6 (17.6)
<i>Follow-up, No. (%)</i>	
Length (mos), median (range)	48 (3 – 106)