Oncologic and Functional Outcomes of Surgical and Nonsurgical Treatment of Advanced Squamous Cell Carcinoma of the Supraglottic Larynx

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IMPORTANCE Nonsurgical treatment of advanced supraglottic laryngeal cancer is widely used as part of a larynx preservation protocol. However, recent studies have suggested that nonsurgical treatment may be associated with inferior survival. Furthermore, it is not clear whether preservation of the larynx provides superior voice or swallowing function in the long term.

OBJECTIVE To test the hypothesis that surgical treatment of advanced-stage squamous cell carcinoma of the supraglottic larynx is associated with superior overall survival (OS), freedom from recurrence (FFR), and noninferior voice and swallowing function.

DESIGN, SETTING, AND PARTICIPANTS Retrospective medical record review of patients treated for stage III or IV squamous cell carcinoma of the supraglottic larynx between January 1990 and June 2013 at a tertiary referral center: 97 patients underwent surgical treatment and 138, nonsurgical treatment. Exclusion criteria included prior definitive treatment for laryngeal cancer or evidence of distant metastatic disease at presentation. The median follow-up for all 235 patients was 63 months.

INTERVENTIONS Surgical or nonsurgical therapy.

MAIN OUTCOMES AND MEASURES Freedom from recurrence (FFR), OS, larynx preservation, voice graded from 1 to 5, and swallowing graded from 1 to 6 using our voice and swallowing function scales.

RESULTS Surgical treatment was associated with superior FFR (5-year FFR: 75% vs 55%; P = .006) but not OS (5-year OS: 52% vs 52%; P = .61). The larynx was preserved in 83% of patients in the nonsurgical group vs 42% of patients in the surgical group (P < .001). Voice function was superior in the nonsurgical group at all time points through 5 years after treatment (mean voice score, 3.8 vs 2.6; P < .001). Swallowing function was comparable between surgical and nonsurgical groups. Multivariable analysis revealed that advanced age (hazard ratio [HR], 1.43 per 10-year increment; 95% CI, 1.19-1.72) and clinical N stage (HR, 1.17 per 1-level increment; 95% CI, 1.05-1.30) were associated with worse OS, while treatment with chemotherapy was associated with superior OS (HR, 0.61; 95% CI, 0.41-0.92).

CONCLUSIONS AND RELEVANCE Compared with surgical treatment, nonsurgical treatment as part of a larynx preservation protocol is associated with a higher likelihood of recurrence but has similar OS and should continue to be viewed as a viable alternative for the treatment of advanced supraglottic laryngeal cancer.

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Management of advanced supraglottic laryngeal cancer is complex, and there is no consensus strategy.1-5 The goals of treatment are cure of disease, with preservation of voice, swallowing, and airway function when possible. Since the seminal Veteran’s Affairs Laryngeal Preservation trial,6 nonsurgical larynx-preserving treatment approaches have been increasingly used, with laryngectomy reserved for salvage of local failure.7,8 Subsequent trials established the superiority of concurrent chemoradiotherapy over radiation therapy (RT) alone or with induction chemotherapy.1,9 However, any direct comparisons of concurrent chemoradiotherapy vs surgery have thus far been limited to retrospective studies.10,11 Unfortunately, the trend toward larynx-preserving management paralleled an increase in mortality from laryngeal cancer,7,12,13 leading some to suggest that survival is being sacrificed for organ preservation.4,8,14-16 Organ-sparing treatment is also associated with significant toxic effects, some of which have been suggested to contribute to the high number of late noncancer deaths noted in patients treated nonsurgically.9,17-19 Moreover, whether anatomic larynx preservation translates to superior voice outcomes in the long term remains to be shown. Consequently, it has been argued that larynx preservation is not worthwhile if survival is compromised, there is no actual functional advantage, or patients succumb to late toxic effects that are attributable to the larynx-preserving treatment.20

Supraglottic squamous cell cancer (SCC) exhibits different biological properties, and select tumors are amenable to organ-preserving surgical options. Some reports show similar survival but better voice outcomes for such treatments compared with total laryngectomy (TL).21-24 Although some studies have examined voice or swallowing function after nonsurgical treatment,9,25-29 few have contrasted the nonsurgical patients with surgically treated patients, and even fewer studies have assessed voice or swallowing function more than 2 years after treatment.

The purpose of the present study was to compare survival, recurrence, larynx preservation, and long-term voice and swallowing function in patients who received surgical vs nonsurgical therapy for advanced supraglottic laryngeal cancer. Multivariable analyses were performed to identify patient, disease, and treatment variables associated with oncologic and functional outcomes. In our discussion, we review the literature to place our findings in clinical context.

Methods

A retrospective medical record review of patients treated for advanced stage SCC of the supraglottic larynx at the Cleveland Clinic was performed with approval of the Cleveland Clinic institutional review board. Inclusion criteria included previously untreated, biopsy-confirmed stage III or IV SCC of the supraglottic larynx presenting between January 1990 and June 2013 and treated with curative intent. We excluded patients with evidence of distant metastasis at presentation. Patients were treated with 1 of the following:

1. Definitive radiation therapy given as 1.8- to 2.0-Gy fractions once daily to a total of 66.0- to 72.0-Gy or 1.2-Gy twice daily to a total dose of 72.0 Gy.
2. Concurrent chemoradiotherapy with the addition of 3 courses of single-agent cisplatin (100 mg/m²/d) given on days 1, 22, and 43; or two 96-hour courses of cisplatin (20 mg/m²/d) plus fluorouracil (1000 mg/m²/d) given during weeks 1 and 4 of definitive RT.30
3. Partial laryngectomy (PL) or TL followed by adjuvant RT to a total of 60 Gy with or without 2 or 3 courses of concurrent cisplatin (100 mg/m²/d) given every 3 weeks during adjuvant RT.

Patients were placed in the nonsurgical group if they received treatment 1 or 2 or the surgical group if they received treatment 3.

Length of follow-up was calculated from the start of definitive treatment. Study data were collected and managed using REDCap electronic data capture tools hosted at the Cleveland Clinic.31 Preexisting comorbidities were recorded, and the Washington University Head and Neck Comorbidity Index was used to estimate the comorbidity score.32,33 Time-to-event outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox results are summarized as the hazard ratio (HR) and its 95% CI. All baseline characteristics were analyzed as univariable prognostic factors. Stepwise analysis was performed to identify multivariable prognostic factors. Because the primary question was to address the effect of definitive therapy, this variable was included in every model whether it was significant or not. Otherwise, nontherapy variables in the multivariable models were significant at P < .05. Chemotherapy and neck dissection were both analyzed as time-varying covariates because they could occur at or after start of definitive therapy. Both voice and swallowing were evaluated by retrospectively scoring physicians’ assessments of the patients’ voice and swallowing as noted in the medical record using our voice and swallowing function scales (Table 1). Repeated-measures analysis of variance was used to identify differences in voice and swallowing score over time. For variables with more than 2 groups, pairwise comparisons were conducted to determine which groups differed if the overall group effect was significant (P < .05).

Supplementary details of treatments, surveillance, data collection and statistical analyses are included in the eMethods in the Supplement.

Results

Patient and Disease Characteristics

The surgical and nonsurgical groups differed in that the nonsurgical group had a greater proportion of African Americans, a higher performance status, lower comorbidity score, higher albumin level, and higher body mass index compared with the patients in the surgical group. Patient characteristics at presentation are summarized in eTable 1 in the Supplement. Clinical T- and N-stage distribution for nonsurgical and surgical groups are detailed in eTables 2 and 3, respectively, in the Supplement. Approximately half of the patients in both
Reasons for Treatment Choice

Reasons for treatment choice are detailed in Table 2. Organ preservation was the most cited reason for patients in the nonsurgical group. When comorbidities were cited as a reason for selection of concurrent chemoradiotherapy, the reason given was poor pulmonary reserve that precluded PL. Of the 53 patients treated with radiation alone, chemotherapy was precluded by comorbidities in 19 patients; 14 patients refused recommended chemotherapy; 6 patients were not recommended chemotherapy because of limited tumor extent; and 14 did not receive chemotherapy because of their medical history. In patients for whom comorbidities were cited as a reason for choice of PL, the predominant comorbidity was poor kidney function contraindicating chemotherapy. Poor kidney function and poor pulmonary reserve were the predominant comorbidities associated with choice of TL. Of the 138 patients in the nonsurgical group, 16 patients experienced notable delay or interruption of radiation treatment and 13 of the 85 patients receiving concurrent chemoradiotherapy experienced notable delay or interruption of chemotherapy treatment.

Table 2. Reasons for Choice of Treatment

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Treatment Type, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT Only</td>
</tr>
<tr>
<td>Organ preservation</td>
<td>70</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>36</td>
</tr>
<tr>
<td>Patient choice</td>
<td>26</td>
</tr>
<tr>
<td>Tumor extent</td>
<td>0</td>
</tr>
<tr>
<td>Poor social support</td>
<td>0</td>
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</tbody>
</table>

Abbreviations: PL, partial laryngectomy; RT, radiation therapy; TL, total laryngectomy.

a The percentage of patients receiving the specific treatment type for whom the corresponding reason was cited. Note that total percentage in each column exceeds 100% because multiple reasons were cited for many patients.

Freedom From Recurrence

In estimating freedom from recurrence, all recurrences (local and/or distant) were counted as events. Surgical treatment (vs nonsurgical) was associated with superior freedom from recurrence. Kaplan-Meier estimates (eFigure 1 in the Supplement) for 5-year freedom from any recurrence were 75% vs 55% in the surgical and nonsurgical groups, respectively (P = .006).

On univariable analysis, advanced clinical N stage (HR, 1.17 per 1 level increment; 95% CI, 1.02-1.33) and poor performance status (HR, 1.92; 95% CI, 1.20-3.07) were associated with a higher risk of any recurrence, while neck dissection was associated with a lower risk of any recurrence (HR, 0.56; 95% CI, 0.36-0.88). Nonsurgical treatment remained associated with a higher risk of any recurrence (HR, 2.25; 95% CI, 1.36-3.74) in multivariable analysis, as did poor performance status (HR, 2.21; 95% CI, 1.37-3.57). Clinical N stage and neck dissection were not significantly associated with freedom from recurrence on multivariable analysis. Race was not associated with risk of recurrence on univariable or multivariable analyses.

Overall Survival

The median overall survival (OS) was 65 months in the nonsurgical group and 64 months in the surgical group (P = .61).522 and Kaplan-Meier estimates of 5-year OS was 52% in both groups (Figure 1). Univariable analysis revealed that advanced age (HR, 1.46 per 10-year increment; 95% CI, 1.21-1.74), poor performance status (HR, 1.62; 95% CI, 1.13-2.32),
Figure 1. Overall Survival in the Nonsurgical and Surgical Treatment Groups

Patients in the nonsurgical treatment group experienced overall survival that was equivalent to those in the surgical treatment group.

Figure 2A shows the mean voice score for the surgical and nonsurgical groups at multiple time intervals. The mean (SD) pretreatment voice score was 3.9 (0.7) in the nonsurgical group and 3.8 (0.9) in the surgery group (P = .29). Patients in the surgery group experienced significant decline in the mean voice function after treatment compared with the pretreatment voice function. When the nonsurgical vs surgery groups were compared, posttreatment voice function is significantly better in the nonsurgical group across all time points after treatment (P < .001). No association was found between posttreatment voice function and sex (P = .45) or marital status (P = .29).

Voice Function

Swallowing Function

Figure 2B shows the mean swallowing score for the 2 groups at intervals. Before treatment, 8 of 130 patients (6%) in the nonsurgical group and 6 of 97 patients (6%) in the surgical group were feeding tube dependent. Of the 130 patients in the nonsurgical group and 97 patients in the surgical group, 14 (10%) and 4 (4%), respectively, had entirely normal swallowing with no symptoms of dysphagia. The mean (SD) pretreatment swallowing score was 4.4 (1.0) in the nonsurgical group vs 4.1 (1.0) in the surgical group (P = .02). In both the nonsurgical and surgical groups, the mean swallowing score declined through 30 days after treatment and then improved through subsequent follow-up. Pairwise comparisons revealed no significant association of posttreatment swallowing function with sex (P = .78), smoking history (P = .17), or marital status (P = .61).

Discussion

In this retrospective study of 235 patients with advanced supraglottic laryngeal cancer who were treated at a single tertiary care institution, the key observations are as follows: (1) Nonsurgical vs surgical treatment was associated with comparable OS in the setting of higher locoregional recurrence among patients treated nonsurgically. (2) Among patients treated with definitive surgical therapy, OS was not significantly different for those treated with TL vs PL. (3) Advanced age, advanced N stage, and not receiving chemotherapy as part of the treatment regimen were associated with worse OS. (4) Nonsurgical treatment was associated with superior voice but comparable swallowing function compared with surgical treatment.
Our finding that survival in the nonsurgical patients was noninferior, even in the face of higher locoregional recurrence, suggests that the salvage laryngectomy is effective at treating local failure without compromising survival. It is consistent with our observation that patients who were salvaged did not have inferior survival compared with those who underwent an initial laryngectomy. Our findings corroborate those of Weber et al\textsuperscript{37} and Forasteire et al\textsuperscript{9} that survival after salvage TL is not influenced by the initial organ preservation treatment. However, these findings are contrary to some recent reports that showed inferior survival in patients treated with definitive radiation or chemoradiation compared with those treated with TL.\textsuperscript{4,5,14,16} The study by Chen and Halpern\textsuperscript{14} included 7019 patients with stage III or IV laryngeal cancer sourced from the National Cancer Database (NCDB). The sheer size of their population confers greater statistical power that could contribute to detection of small differences in survival that was not statistically significant in our smaller study sample. Second, the NCDB cohort includes patients treated at high-volume tertiary institutions and smaller-volume practices. Chen and Halpern\textsuperscript{14} suggested that nonsurgical treatment at lower volume community hospitals might be associated with poorer survival. On the contrary, surgical treatment of more advanced disease tends to be referred to higher volume institutions like ours.\textsuperscript{38} Therefore, our findings may reflect a more balanced comparison of nonsurgical vs surgical treatment in a tertiary care setting, similar to previous clinical trials that compared TL with induction chemotherapy and definitive RT.\textsuperscript{4} Conversely, the external validity of our results may be limited to patients treated in similar tertiary care settings. Finally, our study only includes cancers of the supraglottic larynx. The other studies did not report outcomes stratified by tumor subsite. Inherent differences between supraglottic and glottis disease as well as their response to therapy may contribute to the observed differences. In a study that was limited to supraglottic tumors, Groome et al\textsuperscript{39} concluded that TL was not associated with a survival advantage for stage III disease compared with definitive RT but was associated with a small survival advantage in patients with stage IV disease. Our analysis did not show a statistically significant difference in OS for T4a disease treated surgically vs nonsurgically. This is contrary to prior reports that showed inferior survival for T4a disease treated nonsurgically.\textsuperscript{4-6} Our limited sample size of patients with T4a tumors may be responsible for this discrepancy. Nevertheless, it is reasonable to recommend careful posttreatment follow-up in patients with T4a tumors who receive nonsurgical treatment, given the high likelihood for recurrence among this group and the effectiveness of salvage surgery.

Previously reported 5-year OS for supraglottic laryngeal cancer is between 47% and 56% for stage III disease and 29% and 45% for stage IV disease.\textsuperscript{22,39,40} In our study population of patients with stage III and IV disease, 5-year OS was 55% and 49%, respectively. Our observed OS is similar to what Sessions et al\textsuperscript{22} and Ganly et al\textsuperscript{40} observed in their cohorts of patients treated at single tertiary care institutions and the OS reported in the Department of Veterans Affairs and Radiation Therapy Oncology Group (RTOG) 91-11 trials.\textsuperscript{1,6,9} In contrast, the lower OS reported by Groome et al\textsuperscript{39} was estimated from a population study of cancer registry data. These differences in study population may contribute to the discrepancy in reported OS. Our multivariable analysis showed a strong negative association between clinical nodal stage and OS. The HR for all-cause mortality was 6-fold between cN3 and cN0 disease, corroborating the clinical staging system. Interestingly, Ganly et al\textsuperscript{40} also found clinical N stage and advanced age to be the only factors prognostic of survival in their cohort of patients with advanced supraglottic cancer. Unlike Chen and
Halpern, we did not find race or sex to be associated with survival, perhaps reflecting differences in patient population and practices at a tertiary care institution.

In our population, chemotherapy was used concurrent with radiation as definitive therapy or as adjuvant to surgery. Treatment with chemotherapy was found to be associated with superior OS and freedom from any recurrence but not freedom from distant recurrence. These findings affirm the locoregional control benefit of chemotherapy in treatment of advanced supraglottic laryngeal cancer as previously reported.

We found that OS in patients treated primarily by PL was not inferior to that of patients treated with TL. A key limitation of this comparison is that patients treated with TL had higher T-stage tumors. In fact, patients planned for PL ended up with TL if the tumor extent is noted intraoperatively to be unresectable by PL. Nevertheless, 91% of patients treated with PL remained laryngectomy free through follow-up, suggesting that the surgical larynx preservation options are not inferior to the nonsurgical options with respect to avoidance of TL. This finding may also imply that patients are being selected appropriately for PL vs TL. Similar results have been reported by other groups. Our function scores were graded to capture distinct differences in function such as tracheostomy vs no tracheostomy, with the goals of reliability and low variability. Only a small minority of patients with advanced supraglottic laryngeal cancer are free of dysphonia or dysphagia (8% and 16%, respectively) prior to treatment. Pretreatment voice function was not significantly different between patients who were treated nonsurgically vs those treated with surgery. In both groups, voice and swallowing function were at their worst immediately following treatment. Sessions et al also found that treatment by RT or PL was associated with superior voice outcomes compared with TL but found no association between treatment modality and posttreatment swallowing. Notably, that study did not include patients treated with concurrent chemoradiotherapy. Akst et al found that advanced stage and age were prognostic of poor swallowing after nonsurgical treatment for a variety of head and neck cancers. Salama et al found similar results in their cohort. Both studies included other nonlaryngeal head and neck cancers but not surgically treated patients.

Our study is limited by its retrospective design as well as by instruments that have not been validated. Although we sought to be objective at grading function using instruments that capture distinct functional observations, the retrospective medical record rater was not blinded and is a potential source of bias. In analyzing function scores, we compared means. Statistical validity of this approach depends on the assumption that intervals are equally spaced. In addition, the 14-year study period may include outdated supportive care practices that potentially reduce the validity our conclusions. Nevertheless, our findings are noteworthy and should contribute to the sparse current literature on outcomes after treatment for SCCs of the supraglottic larynx.

Conclusions

When used in appropriately selected patients with advanced supraglottic laryngeal cancer, nonsurgical therapy with laryngectomy reserved for salvage is associated with similar OS as initial surgical treatment. Nonsurgical treatment should be followed by careful surveillance to permit successful salvage surgery for patients who experience recurrence. Chemotherapy administered concurrent with definitive or adjuvant radiotherapy is associated with superior survival and should be strongly advocated as part of the treatment regimen. Non-surgical therapy is associated with superior voice function and comparable swallowing function as surgical treatment. Nonsurgical therapy should continue to be viewed as a viable alternative for the treatment of advanced supraglottic laryngeal cancer.

ARTICLE INFORMATION

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Author Contributions: Drs Elegbede and Burkey had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Elegbede, Adelstein, Kaltenbach, Burkey.

Acquisition, analysis, or interpretation of data: Elegbede, Rybicki, Adelstein, Lorenz, Scharpf, Burkey.

Drafting of the manuscript: Elegbede, Rybicki.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Elegbede, Rybicki, Burkey.

Administrative, technical, or material support: Elegbede, Adelstein, Kaltenbach, Scharpf, Burkey.

Study supervision: Adelstein, Kaltenbach, Lorenz, Scharpf, Burkey.

Conflict of Interest Disclosures: None reported.

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Additional Contributions: Deborah Chute, MD, Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, assisted with identifying study participants; Christine Fleckenstein, Head and Neck Institute, Cleveland Clinic, obtained records of medical data; and Morolake Kuteyi, PharmD, Massachusetts College of Pharmacy and Health Sciences, Worcester, organized data for analysis. Dr Chute, Ms Fleckenstein, and Dr Kuteyi received no financial compensation for their contributions.

REFERENCES


Surgery vs Nonsurgical Therapy for Advanced Supraglottic Laryngeal Cancer


