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Pretreatment computed tomographic gross tumor volume as predictor of persistence of tracheostomy and percutaneous endoscopic gastrostomy tube in patients undergoing larynx preservation

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Abstract

Background.—Although larynx preservation affords patients improvements in laryngectomy-free survival, little has been reported regarding the functional outcomes after larynx preservation. The purpose of this study was to report the predictive value of pretreatment CT-gross tumor volume (GTV) for persistence of tracheostomy and percutaneous endoscopic gastrostomy (PEG) tube in larynx preservation patients.

Methods.—Each patient had a CT scan before initiation of therapy and the GTV was contoured.

Results.—Using recursive partitioning analysis (RPA), threshold GTVs of 27.16 cc and 12 cc were identified for association of time with tracheostomy and PEG tube, respectively. Median (95% confidence interval [CI]) times above and below these thresholds were 1.84 (1.06–not reached [NR]) and 0.75 (0.63–1.26) years, respectively ($p = .03$) for time with tracheostomy and 1.75 (1.34–NR) and 0.84 (0.46–NR) years, respectively ($p = 0.10$) for time with PEG tube.

Conclusion.—This study demonstrates that pretreatment CT-GTV is predictive of an approximately 2.5-fold and approximately 2-fold, respectively, increase in time with tracheostomy and PEG tube.

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Keywords

laryngeal cancer; larynx preservation; functional outcomes; prognosis quality of life

INTRODUCTION

For a number of years, the treatment paradigm for patients with advanced stage squamous cell carcinoma of the larynx was total laryngectomy with possible postoperative radiotherapy.^{1,2} Total laryngectomy is not without significant detriment to quality of life (QOL) as a result of subsequent functional sequelae including: the loss of natural voice, alterations in swallowing function, and the creation of a permanent tracheostoma.^{3,4}

In the early 1990s, the Veterans Affairs Laryngeal Cancer Study established larynx preservation, utilizing chemoradiotherapy (CRT), as an alternative to total laryngectomy in patients with locally advanced laryngeal cancer.⁵ Radiation Therapy Oncology Group 91-11 demonstrated that treatment with concurrent CRT led to reasonable laryngectomy-free survival rates at 5 and 10 years of 47% and 23.5%, thus furthering support of a larynx preservation approach.^{6,7} Since these 2 landmark trials, definitive concurrent CRT has become the standard of care for many patients with locally advanced laryngeal cancer.

Larynx preservation, however, is not without its own set of impairments to the QOL of patients. Indeed, the persistence of tracheostomy and of percutaneous endoscopic gastrostomy (PEG) tube after larynx preservation has been shown to result in poor functional outcomes and a decreased QOL.^{8,9} Keeping this in mind, we sought to evaluate our institutional data of patients with locally advanced laryngeal cancer undergoing definitive concurrent CRT for factors predictive for persistence of both tracheostomy and PEG tube.

MATERIALS AND METHODS**Patient characteristics**

An institutional review board approved retrospective chart review was performed for patients with stage III and IV locally advanced laryngeal cancer treated with definitive concurrent CRT between January 2005 and June 2012. These patients were retrospectively restaged according to the American Joint Committee on Cancer, seventh edition. Initial evaluation of all patients included a thorough history, physical examination, fiber-optic laryngoscopy, esophagoscopy, bronchoscopy, and CT and/or MRI of the neck. Positron emission tomography was not routinely performed. Each patient had a CT scan before initiation of therapy. All patients were discussed in a multidisciplinary tumor board consisting of oncologic otolaryngologists (ear, nose, and throat specialists), medical oncologists, radiation oncologists, and neuroradiologists, in which a consensus treatment decision was reached. Patient gross tumor volume (GTV), defined as the volume of primary tumor assessed on CT, was retrospectively contoured utilizing the Eclipse treatment planning software. Patient characteristics are summarized in Table 1.

Treatment

Treatment consisted of larynx preservation with definitive concurrent CRT. Radiotherapy was delivered using 3-field or intensity-modulated radiotherapy to a prescribed dose of 66 to 72 Gy. Most patients received platinum-based chemotherapy during radiation, with patients receiving up to 3 cycles. Placement of the tracheostomy and PEG tube were at the discretion of the treating ear, nose, and throat specialist when there was concern of airway obstruction, severe dysphagia, or malnutrition. Placement of prophylactic tracheostomy or PEG was not routinely performed. Patients were encouraged to follow-up with speech and swallowing therapists after CRT where the degree of dysphagia was assessed with modified barium swallow. Treatments for dysphagia included esophageal dilation, Botox injections, and swallowing exercises. Treatment characteristics are summarized in Table 2.

Follow-up

At completion of therapy, patients were typically evaluated on a monthly basis for the first year, every 2 to 3 months in the second year, every 3 to 6 months in years 3 through 5, and yearly thereafter. Follow-up evaluations consisted of a comprehensive history and physical examination, which included flexible laryngoscopy. CT of the neck and chest were performed within 6 months of CRT completion and then yearly thereafter, unless prompted by objective findings. Those patients with radiographic or suspicious physical examination findings proceeded to direct biopsy. Patients demonstrating pathologically confirmed local recurrences were then evaluated for salvage laryngectomy, palliative chemotherapy, or best supportive care.

Statistical analysis

The Fisher exact tests and t tests were used to evaluate the difference between tracheostomy and PEG tube endpoints for continuous and categorical variables, respectively. The Kaplan–Meier method and Cox regression were used to estimate survival distributions and hazard ratios, respectively, for the time with tracheostomy or PEG tube endpoints, with events being censored at the time of removal or last known follow-up. Overall disease status (no evidence of disease or residual disease) was not taken into consideration with regard to time with tracheostomy and PEG tube. Because of skewness in the GTV variable, it was log-transformed for analysis purposes. Recursive partitioning analysis (RPA) was performed to identify a threshold for GTV for both endpoints, using the `rpart` function from the “`rpart`” version 4.1–1 package in R version 3.0.1.^{10,11} As the sample size was small, we did not keep any holdout sample. The defaults for the `rpart` function were used, including the requirement that 7 observations were required in each daughter node with a complexity parameter of 0.01.

RESULTS

There were 75 patients in the cohort. The median age of the entire cohort was 58 years. There were 60 men (80%) and 15 women (20%). Forty-seven patients had a tracheostomy placed, 47 had a PEG tube placed (3 posttreatment), and 35 patients had both a tracheostomy and PEG tube placed. GTV information was available for 41 patients.

Tracheostomy was placed in 71% of patients with T3/T4 versus 37% of patients with T1/T2 disease ($p = .01$). Placement was noted in 76% of patients with hemilarynx fixation versus 49% without ($p = .03$). A significant difference in $\log_{10}$ -transformed GTV existed between patients with and without tracheostomy placement, 1.24 versus 0.96 ($p = .002$). RPA revealed a threshold GTV of 27.16 cc for association of time with a tracheostomy. Patients with less than this threshold had a median (95% confidence interval [CI]) time with tracheostomy of 0.75 (0.63–1.26) versus 1.84 (1.06, not reached [NR]) years for patients above this threshold ($p = .03$; see Figure 1). As of their last follow-up, 38% of the patients still had their tracheostomy. Median overall survival (95% CI) in patients with and without tracheostomy was not statistically different, 3.2 (2.3, NR) versus 4.1 (3.0, NR) years (Figure 2; $p = .54$).

A PEG tube was placed in 63% of patients with T3/T4 versus 63% of patients with T1/T2 disease ($p = 1.00$). Of patients whose weight was known at diagnosis, it was found to be statistically significant for placement of a PEG tube ($p = .001$). A significant difference in $\log_{10}$ -transformed GTV existed between patients with and without PEG tube placement, 1.20 versus 0.96 ($p = .004$). A PEG tube was placed in 75% of patients with supraglottic versus 41% with glottic cancer ($p = .007$). Patients with nodal disease were also more likely to have a PEG tube placed than those without (85% vs 45%; $p = .001$). In the 47 patients with PEG tubes, N2c/N3 nodal status was significantly associated with the time with the PEG tube ($p = .005$). N2c/N3 nodal status remained significant on multivariable analysis. Median time to PEG tube removal for patients with less than N2c/N3 disease was 0.85 (0.61, NR) years compared to those with N2c/N3 disease was NR (NR, NR). RPA revealed a threshold tumor volume of 12 cc for association with time with a PEG tube. Patients with less than this threshold had a median time with a PEG tube of 0.84 (0.46, NR) versus 1.75 (1.34, NR) years for patients above this threshold ($p = .10$; see Figure 3). As of their last follow-up, 51% of the patients still had their PEG tubes in place. Median survival in patients with and without PEG tubes was 3.04 (2.62, NR) versus 4.95 (3.28, NR) years (Figure 4; $p = .50$).

DISCUSSION

We demonstrate here that the pretreatment CT-GTV is predictive of an approximately 2.5-fold and approximately 2-fold, respectively, increase in length of time with a tracheostomy and a PEG tube — 2 surrogates for poor functional outcomes and reduced QOL.^{8,9} Furthermore, we identify N2c/N3 nodal status as significantly associated with length of time with a PEG tube.

Patient functional outcomes and impairments to QOL after larynx preservation are garnering more attention.^{8,9,12–15} However, the reporting of outcomes across studies is often incongruent, with little uniformity in follow-up times, evaluation tools, and reliability of assessments.¹⁵ Nevertheless, identifying factors, or their surrogates, predictive of QOL will help to guide treatment decisions.

Patient-reported outcomes for speech and swallowing were described in the recent update of the Radiation Therapy Oncology Group 91–11 trial.⁷ Only 4% to 8.5% of patients in the

concurrent CRT arm noted moderate difficulty with speech and voice quality, whereas swallowing dysfunction was described in 17% to 24%.⁷ In support of these findings, an analysis of 43 patients treated with larynx preservation for voice and deglutition differences concluded that these patients had mild to moderate voice and swallowing abnormalities.¹²

Further evidence is demonstrated in a study evaluating the clinical predictors of QOL in patients with head and neck cancer.⁹ Respondents noted the presence of a PEG tube as the strongest predictor, whereas the presence of a tracheostomy and history of CRT were classified as moderate predictors of QOL.⁹ Interestingly, laryngectomy and neck dissection were among the weakest predictor variables for QOL.⁹ Another study of 60 patients evaluated factors predictive of persistence of tracheostomy after concurrent CRT and found that T3/T4 status and hemilarynx fixation at the time of presentation as being associated with persistence of tracheostomy 6 and 12 months posttreatment.¹³ In addition, they found that 12-month mortality was higher in patients with T3/T4 disease who received pretreatment tracheostomy.¹³ Although we identified T3/T4 status ($p = .01$) and hemilarynx fixation ($p = .03$) as factors predictive of placement of tracheostomy, these factors were not significant for persistence of tracheostomy posttreatment.

Our study was not without limitations. Certainly, with only 41 samples analyzed in a retrospective fashion, over-fitting to the analysis database is possible (and perhaps likely). This analysis was not meant to forge a new treatment paradigm but rather provoke a more careful examination of all parameters during patient care, which may lead to better patient outcomes. Other databases can be used to replicate or refute the results that we have shown here. In addition, the numbers of patients with T1/T2 disease compared with patients with T3/T4 disease is small. Furthermore, a relatively high number of patients with T1/T2 disease received a tracheostomy (37%), which we attribute to bulky lymphadenopathy and/or T2 glottic cancer with hypomobile vocal cords. In addition, although patients were encouraged to follow-up with speech and swallowing professionals, compliance was not documented. Furthermore, pretherapy and posttherapy modified barium swallow and/or videostroboscopic data was not available/not performed in the majority of our patients.

Further study is warranted to evaluate and standardize the patient and disease-specific factors, or their surrogates, which predict for poor functional outcomes and decreased QOL in patients undergoing larynx preservation. Once known, these factors will help guide treatment decision-making.

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FIGURE 1.
Time with tracheostomy based on recursive partitioning analysis threshold. GTV, gross tumor volume.

FIGURE 2.
Overall survival with and without tracheostomy (trach).

FIGURE 3.
Time with percutaneous endoscopic gastrostomy (PEG) tube based on recursive partitioning analysis threshold. GTV, gross tumor volume.

FIGURE 4.
Overall survival with and without percutaneous endoscopic gastrostomy (PEG) tube.

TABLE 1.

Patient characteristics.

Characteristic	No. of patients
Age, y	
Median	58
Range	33.6–79.4
Sex (%)	
Male	60 (80)
Female	15 (20)
T classification, %	
1	2
2	17
3	37
4	19
N classification, %	
0	42
1	4
2	28
3	1
Primary tumor site, %	
Supraglottic	48
Glottic	27

TABLE 2.

Treatment characteristics.

Treatment	No. of patients (%)
Up-front neck dissection	4 (5.3)
Concurrent chemotherapy	
Platinum-based alone	51 (68.0)
Erbix alone	11 (14.6)
Platinum ×1 then erbitux	4 (5.3)
Other	2 (2.7)
None	7 (9.3)
Tracheostomy placement before CRT	47 (62.7)
Yes	42 (56)
No	5 (6.7)
Prophylactic PEG placement	46 (61.3)
Yes	21 (28)
No	25 (33.3)

Abbreviations: CRT, chemoradiotherapy; PEG, percutaneous endoscopic gastrostomy.