Chemoradiation for patients with large-volume laryngeal cancers

Kerstin M. Stenson, MD,[1]* Ellen MacCracken, MS CCC-SLP,[1] Rangesh Kunnavakkam, MPH,[2] Ezra E. W. Cohen, MD,[3] Louis D. Portugal, MD,[1] Victoria Villaflor, MD,[3] Tanguy Seiwert, MD,[3] Elizabeth Blair, MD,[1] Daniel J. Haraf, MD,[4] Joseph K. Salama, MD,[4,5] Everett E. Vokes, MD[3]

[1]Department of Surgery, Section of Otolaryngology/Head and Neck Surgery, University of Chicago, Chicago, Illinois, [2]Health Science Division, University of Chicago Chicago, Illinois, [3]Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, Illinois, [4]Department of Radiation and Cellular Oncology, University of Chicago, Chicago, Illinois, [5]Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina.

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ABSTRACT: *Background.* Patients with T4 laryngeal cancers, including those with large-volume (cartilage or tongue-base invasion) lesions, are often excluded from organ-preservation trials due to expectations of inferior outcome in terms of survival and function. We hypothesize that such patients indeed have acceptable survival and function when treated with organ-preservation strategies.

Methods. Retrospective analysis of prospectively collected data of a cohort of patients with T4 laryngeal cancer was carried out. Follow-up ranged from 0.18 to 15.6 years. All T4 laryngeal cancer patients who were enrolled in the University of Chicago concomitant chemoradiotherapy protocols from 1994 to the present were reviewed. This study was composed of 80 newly diagnosed T4 laryngeal cancer patients. Efficacy of treatment was determined through evaluations of survival and function. Survival was evaluated via Kaplan–Meier methods. Swallowing function was evaluated by an oropharyngeal motility (OPM) study and swallowing scores were assigned. Higher scores reflected increasing swallowing dysfunction.

Results. Fifty-five of 80 patients (~69%) had documented large-volume tumor. Two- and 5-year overall survivals were 60.0% and 48.7%, respectively. Disease-specific 2- and 5-year survivals for the group were 80.1% and 71.3%, and 79.4 and 74.3%, respectively, for the 55 patients with large volume status. Progression-free survival rates were 52.6% and 47.6%. Forty-four of 65 patients (~68%) with OPM data had a Swallowing Performance Status Scale (SPSS) score of $\leq$5, indicating various degrees of swallowing abnormalities not requiring a gastrostomy tube. This is a functional-preservation rate of 67.7%.

Conclusions. Chemoradiation for patients with T4 laryngeal cancer appears to be an effective and reasonable option, particularly in light of the satisfactory survival and function-preservation rates. © 2011 Wiley Periodicals, Inc. *Head Neck* **34:** 1162–1167, 2012

KEY WORDS: laryngeal cancer, organ preservation, head and neck cancer, swallowing function, disease-specific survival

The publication of the now landmark Veterans' Affairs Laryngeal trial in 1991 was significant for head and neck cancer specialists and patients alike.[1] It was the first robust study that showed the feasibility of larynx preservation without compromise in survival. Since that time, concurrent chemoradiation regimens have become the most widely applied nonsurgical strategy for larynx preservation in patients with advanced laryngeal cancer.[2] Many patients with advanced head and neck cancer have achieved profound benefit from these function-preserving multimodality treatments.

Despite these advances, patients with T4 laryngeal cancers, including those classified with large volume (cartilage or tongue-base invasion) are often excluded from organ-preservation trials. Indeed, National Comprehensive Cancer Network (NCCN) guidelines reserve clinical trials or concurrent chemoradiotherapy only for those patients with T4a glottic and supraglottic who decline total laryngectomy.[3] These recommendations arise from the dogmatic belief that cartilage penetration portends increased risk of chondroradionecrosis and inferior response if (chemo)radiotherapy is used for cure. Poor function and worse survival due to lack of efficacy are expected.[4–7]

Despite these beliefs, head and neck cancer specialists have applied multimodality organ-preservation principles to patients with advanced laryngeal cancer, with variable and sometimes contrary results.[8–11] The purpose of this present study was to analyze efficacy, survival, and swallowing function in such patients, in particular patients with large-volume laryngeal cancer, treated with definitive-intent concurrent chemoradiotherapy.

***Corresponding author:** K. M. Stenson, Department of Surgery, Section of Otolaryngology/Head and Neck Surgery, University of Chicago, Chicago, Illinois. E-mail: kstenson@surgery.bsd.uchicago.edu

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MATERIALS AND METHODS

Patient population

This is a retrospective analysis of prospectively collected data. All T4 laryngeal cancer patients who were enrolled in University of Chicago concomitant chemoradiotherapy protocols from 1994 to present were reviewed. This included analysis of 13 consecutive clinical trials and 996 newly diagnosed patients with locoregionally

TABLE 1. Swallowing Performance Status Scale (SPSS) scoring.

Score	Description
1. Normal	
2. WFL	Abnormal oral or pharyngeal stage but able to eat regular diet without modifications or swallowing precautions
3. Mild impairment	Mild dysfunction in oral or pharyngeal stage, requires modified diet without need for therapeutic swallowing precautions
4. Mild–moderate impairment with need for therapeutic precautions	Mild dysfunction in oral and pharyngeal stage, requires modified diet and therapeutic precautions to minimize aspiration risk
5. Moderate impairment	Moderate dysfunction in oral or pharyngeal stage, aspiration noted on exam, requires modified diet and swallowing precautions to minimize risk of aspiration
6. Moderate–severe impairment and requires supplemental enteral feeding support	Moderate dysfunction in oral or pharyngeal stage, aspiration noted on exam, requires modified diet and swallowing precautions to minimize risk of aspiration, needs supplemental feeding support
7. Severe impairment	Severe dysfunction with significant aspiration or inadequate oropharyngeal transit to esophagus, NPO, requires primary enteral feeding support

Abbreviations: WFL, within functional limits; NPO, nothing by mouth (L. nil per os).

advanced head and neck cancer. Patients were included in this analysis if they had laryngeal carcinoma classified as T4 with the appropriate American Joint Committee on Cancer (AJCC) staging manual of the time of the study date. No patients with T4 laryngeal cancer were excluded. CT scans were reviewed when available to document large-volume status. All study protocols underwent Institutional Review Board approval and each patient signed informed consent for each protocol.

Treatment regimens

All chemotherapeutic regimens involved concomitant chemoradiotherapy, with or without induction chemotherapy. Agents included 5-fluorouracil and hydroxyurea, with paclitaxel, docetaxol, carboplatin, cisplatin, or others as a third agent. Some protocols treated patients with cisplatin-based regimens delivered with accelerated concomitant boost radiotherapy. In accord with protocol, some patients were given induction chemotherapy, usually carboplatin and paclitaxel sometimes including gefitinib or cetuximab. Most patients were treated with 5 to 7 cycles of 5-fluorouracil and hydroxyurea (FHX-based) chemoradiotherapy consisting of 5 days of concurrent continuous infusion FHX and once or twice daily RT (1.5 Gray [Gy] twice a day or 2 Gy four times/day) followed by 9 days without any treatment. Total radiation dose was 70 to 75 Gy and the radiation dose/techniques varied over the years. Conventional radiotherapy was used prior to 2000. Two-dimensional treatment planning was used prior to 1998, at which point 3-dimensional planning ensued with the use of the CT simulator. After 2000, intensity-modulated radiotherapy (IMRT) was used. Doses to all uninvolved at-risk nodal groups and microscopic disease varied, depending on the year and the protocol. In older studies, the dose to low-risk microscopic disease was 50 Gy once daily. The dose to high-risk microscopic disease was 60 Gy. With the start of twice-daily radiation, the dose was 1.5 Gy twice a day. Low-risk microscopic disease received between 36 to 45 Gy based on the protocol. High-risk microscopic disease received between 51 and 60 Gy, depending on the protocol. Gross disease received 75 Gy. Although the chemotherapeutic drug types, radiation dosage, and protocol specifics varied over the 16-year period of the present study, the chemoradiation paradigm remained constant. In brief, concurrent chemoradiation delivers high locoregional control by taking advantage of the radiosensitizing effects of the chemotherapeutic agent. At the same time, active drugs are delivered systemically, potentially eradicating micrometastatic disease. Throughout this era, the studies have focused on survival as well as organ/function preservation through the reduction of acute and chronic side effects, use of novel agents, and through deintensifying radiation dose.

Follow-up

Patients were followed every 2 months for the first year, every 3 to 4 months for the second year, and every 6 to 12 months thereafter. CT scans of the head, neck, and chest were completed every 3 to 6 months. Patients would often undergo biopsy of the primary site 1 to 3 months following therapy completion to verify complete response. Patients with N2 or greater neck disease, or those with less than a complete radiologic response, often underwent planned neck dissection.

Swallowing function evaluation

Patients underwent oropharyngeal motility study before and after treatment. Oropharyngeal motility (OPM) is a

TABLE 2. Demographics of 80 patients with T4 laryngeal cancer treated with concurrent chemoradiotherapy, 1994–2009.

Characteristic	No. of patients (%)
Sex	
Male	55 (27.6)
Female	21 (72.4)
Race	
African-American	46 (60.5)
White	29 (1.3)
Hispanic	1 (38.2)
Site	
Supraglottis	64 (16.2)
Glottis	13 (80.0)
Subglottis	3 (3.8)
Large-volume status	
Present	55 (68.8)
No information or absent	25 (31.2)
Nodal status	
N0–N1	51 (64.0)
N2a–N2b	11 (14.0)
N2c	14 (17.0)
N3	4 (5.0)

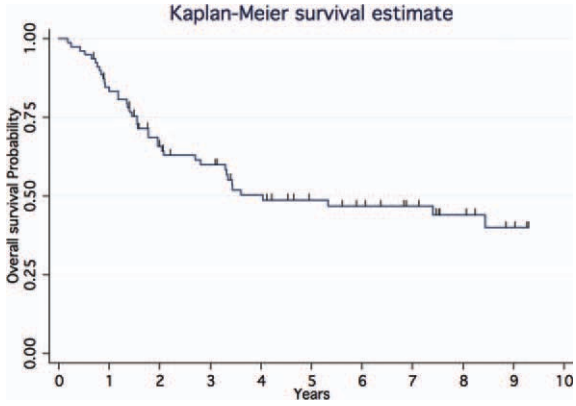

FIGURE 1. Overall survival of 80 patients with T4 laryngeal cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

videofluoroscopic evaluation that documents and quantifies several (27 in number) functional parameters, such as oral transit time, pharyngeal impairment, and presence of aspiration. These parameters are then calculated into the Swallowing Performance Status Scale (SPSS) score, ranging from 1 to 7 (Table 1). Our institution has found that the SPSS score is a clinically valid tool and provides an accurate global measure of swallowing function. Higher scores reflect increasing swallowing dysfunction. Because patients typically underwent multiple OPM studies, the SPSS score of the last recorded study was noted in the database.

Survival: statistical methods

Progression-free survival, overall survival, and disease-specific survival were calculated by the Kaplan–Meier product limit estimate. Overall survival was measured from the date of study entry to the date of death due to any cause. Patients who had not died or who were lost to follow-up were censored for overall survival when they were last known to be alive. Progression-free survival was measured from the date of study entry to first evidence of disease recurrence or death due to any cause. Patients who were alive and who had not experienced disease progression, or who were lost to follow-up, were censored for progression-free survival at the date that they were last known to be alive and progression free. Disease-specific survival was measured from date of study entry to the date of death due to the complication of the disease. Patients who died due to other causes were censored and patients who were alive or who were lost to follow-up were censored for disease-specific survival when they were last known to be alive. Deaths due to toxicity and deaths due to other causes were also estimated. In addition, large-volume status was correlated with swallowing and survival functions.

RESULTS

Demographics

Eighty newly diagnosed patients with T4 laryngeal cancer were identified. In all 58 patients were treated prior to 2002 and 22 patients were treated after 2002. Fifty-five of these patients had documented large-volume tumor via tongue base extension (20), cartilage erosion (35), extension into soft tissues of the neck (14), or extension into the esophagus (1). Several patients had a combination of these factors. There were 55 men and 21 women treated (4 patients without this data). Follow-up ranged from 0.18 to 15.6 years, with a mean of 4.09 years. One patient had incomplete follow-up data. The average age was 58 (range, 33–84 years) and the major laryngeal subsite was supraglottis (64 of 80 patients) (Table 2). Of the 80 patients with T4 laryngeal cancer, 17 patients had neither CT film nor report for review. Six patients had reports that did not clearly indicate why the patient was given T4 designation. Of the 57 remaining patients, 30 had CT films for review in the electronic medical record, whereas 27 patients (mostly those treated prior to 1999) had only CT scan reports for review. Laryngeal cancer staging criteria for AJCC 1992, 1997, 2002, and 2010 were reviewed. Based on this information, the 55 patients classified as large-volume status would be categorized as having T4 cancers throughout the study time period.

Survival

Entire group. Two- and 5-year overall survival rates were 65.8% and 48.7% (Figure 1). Disease-specific 2- and 5-

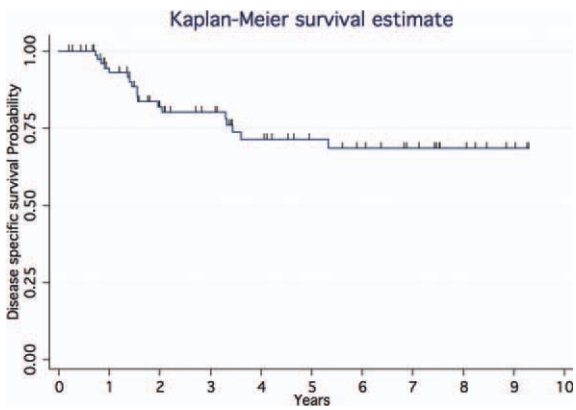

FIGURE 2. Disease-specific survival of 80 patients with T4 laryngeal cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

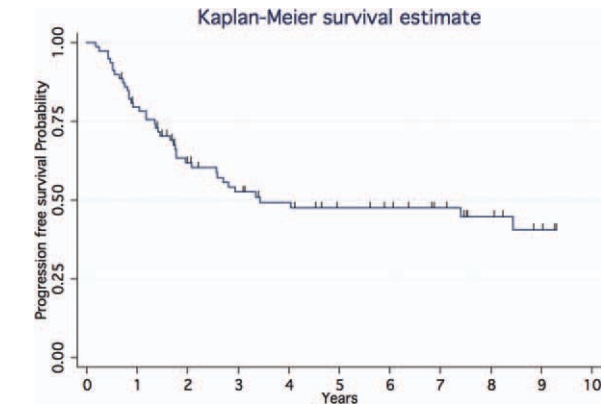

FIGURE 3. Progression-free survival of 80 patients with T4 laryngeal cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

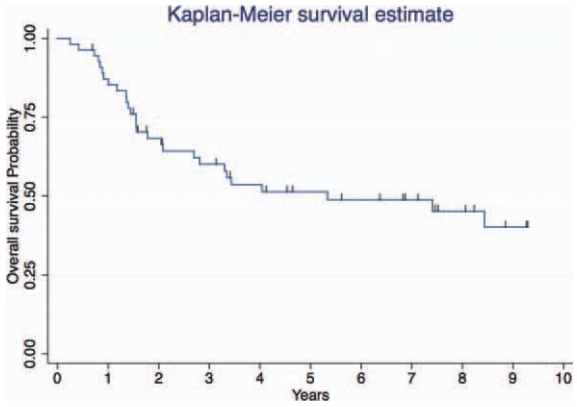

FIGURE 4. Overall survival of patients with large-volume status. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

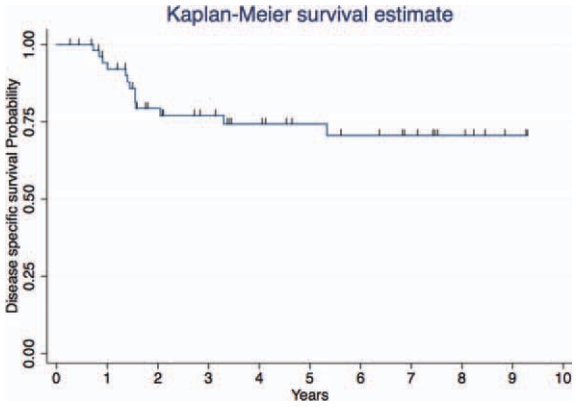

FIGURE 5. Disease-specific survival of patients with large-volume status. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

year survival rates were 81.9% and 71.3% (Figure 2). Progression-free survival rates were 61.9% and 47.6% (Figure 3).

Large-volume status. Two- and 5-year overall survival rates for patients with large-volume status were 68.3% and 51.3% (Figure 4). Disease-specific 2- and 5-year survival rates for patients with large-volume status were 79.4% and 74.3%, respectively (Figure 5). Ten patients underwent salvage laryngectomy (larynx-preservation rate, 87.5%), 1 for aspiration and 9 for persistent/recurrent cancer. Two of these patients are alive, 1 patient died of a second primary, and 6 patients succumbed to metastatic disease.

Swallowing function. Sixty-five patients had pretreatment oropharyngeal motility studies. The pretreatment oropharyngeal motility mean, median, and mode scores are 4.2, 4, and 4. There were 2 patients with an SPSS score of 1, 12 with a score of 2, 10 with a score of 3, 13 with a score of 4, 11 with a score of 5, 9 with a score of 6, and 8 patients with an SPSS score of 7. The posttreatment oropharyngeal motility mean, median, and mode scores were 4.9, 5, and 4 for 65 patients. There was 1 patient with an SPSS score of 1, 1 with a score of 2, 9 with a score of 3, 17 with a score of 4, 16 with a score of 5, 9 with a score of 6, and 12 patients with an SPSS score of 7. The mean length of time between pretreatment and posttreatment OPM study was 27.6 months. Our analysis showed that 44 of 65 patients had an SPSS score of ≤ 5, indicating various degrees of swallowing abnormalities *not* requiring a gastrostomy tube. This is a functional-preservation rate of 67.7%. Of the 65 posttreatment OPM studies, 22 patients were documented to have a tracheotomy. Six of these patients went on to have salvage

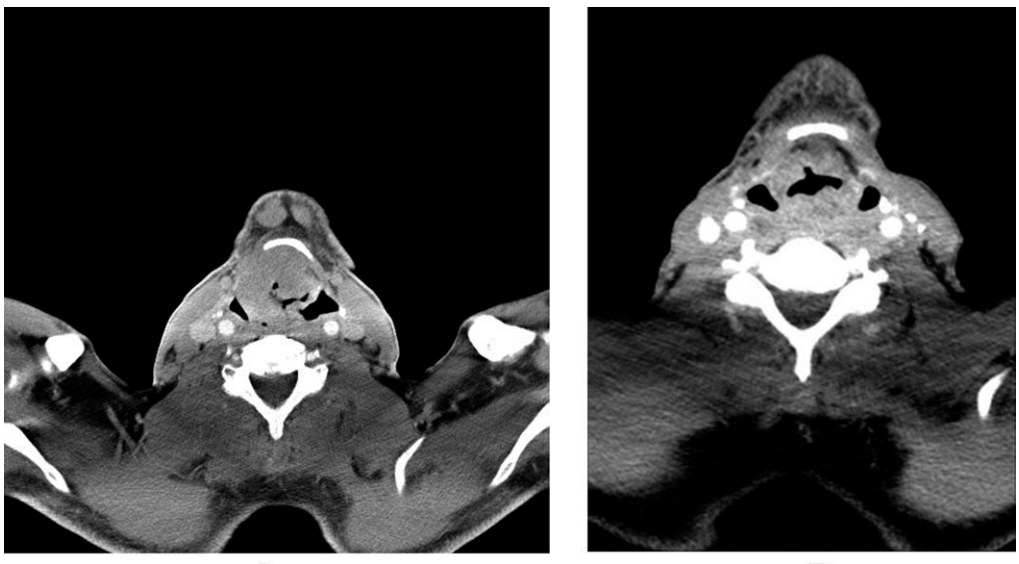

FIGURE 6. Patient with large-volume laryngeal cancer before chemoradiation (A: October 2007) and after (B: March 2009).

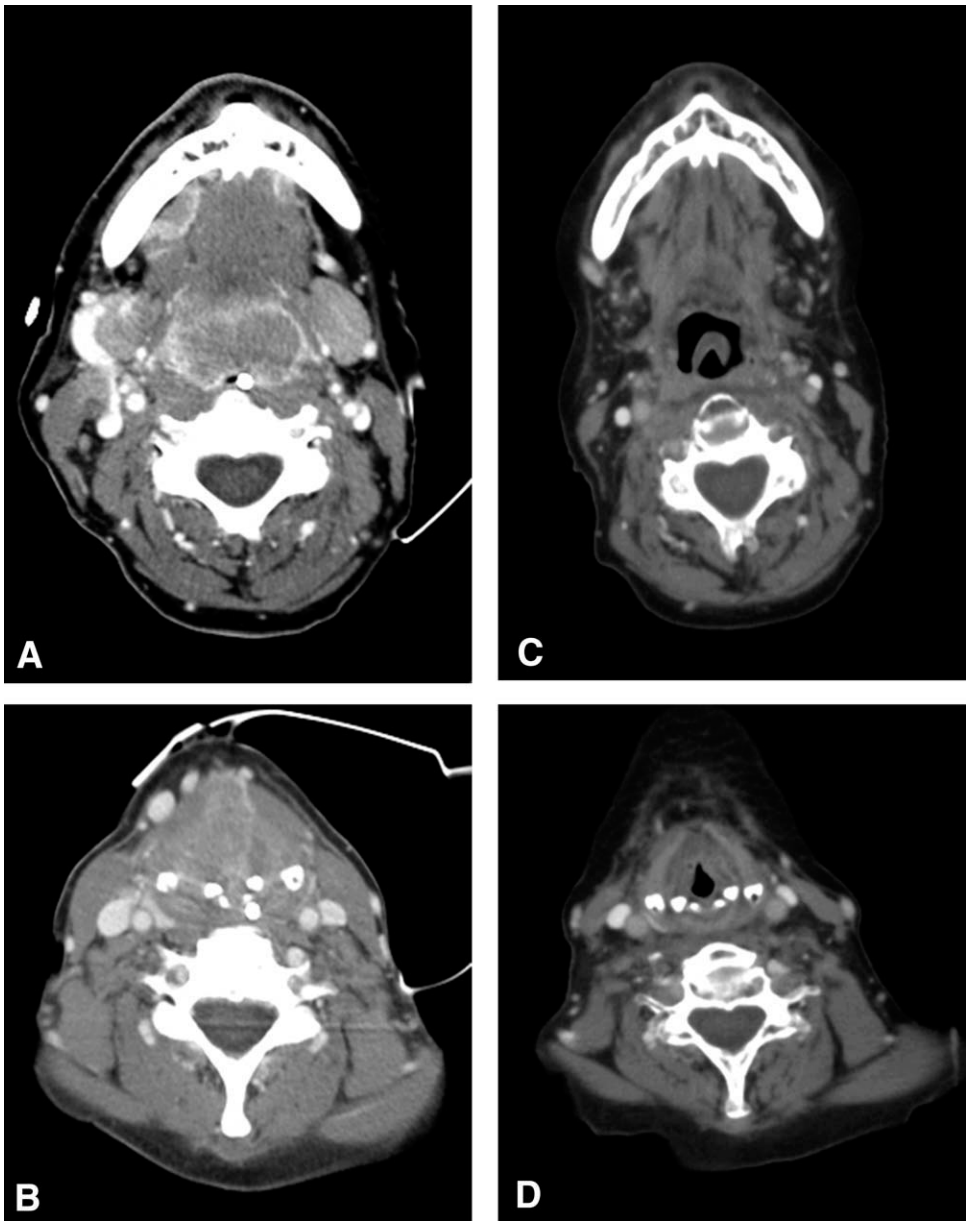

FIGURE 7. Patient with large-volume laryngeal cancer treated with chemoradiation before (A, B: March 2002) and after (C, D: November 2009) treatment. Patient was decannulated December 2002.

laryngectomy, leaving 16 with possible permanent tracheotomy.

DISCUSSION

Great advances have been made for many patients with advanced head and neck cancer. Although patients with large-volume laryngeal cancer traditionally have been excluded from organ-preservation protocols, the University of Chicago Head and Neck Cancer Team possesses a record of treating such patients with curative-intent chemoradiation (see Figures 6 and 7).[8] Others have proposed a like-minded philosophy, in that the presence of cartilage or bone invasion should not be a contraindication for enrollment in a chemoradiation regimen.[10,11] The University of Chicago embraces this approach, saving laryngectomy for intractable aspiration or salvage of recurrent/persistent disease. Our survival parameters are in accord with other series of patients with laryngeal cancer who have undergone chemoradiation.[9,12] In particular, disease-specific survivals in our and others' series are improved compared with a recent large-scale study of survival in patients with laryngeal cancer.[13] This may be due to differing patient populations or institutional experiences, or the use of concurrent versus sequential chemoradiation.

Our functional results show that most patients displayed significant swallowing abnormalities before and after chemoradiation treatment. Importantly, the objective

measure of the SPSS score showed that most had SPSS scores of ≤ 5 and were able to function without the use of a gastrostomy tube.

The swallowing outcomes are strongly related to the critical role of the speech therapist in providing aggressive swallowing therapy. Swallowing therapy with the use of compensatory diet and strategic techniques, along with close monitoring of pulmonary status and nutrition, likely resulted in optimal swallowing performance.

Several authors have studied predictors of outcome (survival or functional) in patients undergoing nonoperative treatment for advanced laryngeal cancer, including vocal cord fixation, tumor volume, and chemoselection.[14–16] Although there appears to be evidence that positively correlates large tumor volume with lower survival, there have been no validated markers that have been found to reliably predict outcome of larynx-preservation strategies.[4] Our data, like those of others, suggest that the overall biology of the disease, and not necessarily extent of tumor, plays a significant role in outcome in patients undergoing chemoradiation for T4 laryngeal cancers.[11]

The critiques of our study include the inherent challenges associated with a retrospective analysis. In addition, due to the timespan of the study period, precise staging of T4 laryngeal cancers had evolved. What was once considered a T4 lesion, based on inner cortex erosion, is currently classified as a T3 lesion. It is possible that our survival results were influenced by this modification in T-staging, although all 55 of large-volume patients would have qualified for AJCC 2010 T4 classification. Although MRI is thought to be the best method to detect cartilage invasion in laryngeal cancer, many centers rely on CT scanning for practical reasons. Criteria for CT diagnosis of cartilage invasion include extralaryngeal tumor spread, sclerosis of cartilage, or lysis/erosion of cartilage.[17] There are inevitable false-positive results due to peritumoral inflammation.

Another critique of our study is lack of data regarding voice quality and the presence of tracheotomy. Our databases did not consistently record these measures, especially in the earlier years of the study. In the past 5 to 7 years, a Performance Status Scale for Head and Neck Cancer Patients (PSSHN) has been developed for clinician-rated assessment of performance status in this group. The PSSHN includes assessment of understandability of speech, normalcy of diet, and eating in public. It has demonstrated inter-rater reliability, discriminant validity, and expected correlations with different subscales of the FACT–H&N (Functional Assessment of Cancer Therapy–Head and Neck) in samples with a range of head and neck cancer diagnoses. There were 19 patients with complete PSSHN data. Seventeen of 19 (89.5%) had an understandability-of-speech score of 100%, although voices ranged from normal to harsh, breathy, wet voice quality. One person was aphonic (score 0%) and 1 person had a score of 25% (poor speech intelligibility).

Finally, an observer may be critical of the current data if viewed in light of a 33% incidence of permanent G-tube (vs 67% of patients who are G-tube-free). The potential social stigma of a laryngectomee compared with that of a patient who is unable to eat orally/G-tube dependent, without a stoma, is a subjective factor for each patient and surgeon, and central to all of head and neck specialists' efforts to improve patients' quality of life. At this time, there are solid data in the literature that indicate better quality of life in patients with advanced laryngeal cancer who are treated with chemoradiation.[18,19]

CONCLUSIONS

Optimizing survival and functional outcomes for patients with advanced laryngeal cancer depend heavily on patient selection and the firm realization that no treatment modality is ideal for every patient.[2] Imperative to all head and neck surgeons and oncologists is individual planning and thorough counseling of each patient. Our data indicate that chemoradiation represents an effective option for patients with T4 laryngeal cancer, including those with large-volume status. In general, this group has not been historically offered organ-preservation treatment. Chemoradiation appears to be an effective and reasonable alternative for these patients, particularly in light of the satisfactory survival and function.

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