Published in final edited form as:

Oral Oncol. 2018 April ; 79: 1–8. doi:10.1016/j.oraloncology.2018.01.025.

Three-Dimensional Imaging Assessment of Anatomic Invasion and Volumetric Considerations for Chemo/Radiotherapy-Based Laryngeal Preservation in T3 larynx Cancer

Mona Kamal, M.D, Ph.D^{1,2}, Sweet Ping Ng, MBBS, FRANZCR¹, Salman A. Eraj, BA^{1,3}, Crosby D. Rock, BS^{1,4}, Pham Brian, BS¹, Jay A. Messer, M.D^{1,5}, Adam S. Garden, M.D¹, William H. Morrison, M.D¹, Jack Phan, M.D, Ph.D¹, Steven J. Frank, M.D¹, Adel K. El-Naggar, M.D., Ph.D⁶, Jason M. Johnson, M.D⁷, Lawrence E. Ginsberg, M.D⁷, Renata Ferrarotto, M.D⁸, Jan S. Lewin, Ph.D⁹, Katherine A. Hutcheson, Ph.D⁹, Carlos E Cardenas, MS¹⁰, Mark E. Zafereo, M.D⁹, Stephen Y. Lai, M.D, Ph.D⁹, Amy C. Hessel, M.D⁹, Randal S. Weber, M.D⁹, G. Brandon Gunn, M.D¹, Clifton D. Fuller, M.D, Ph.D^{1,11}, Abdallah S. R. Mohamed, M.D, MSc^{1,11,12}, and David I. Rosenthal, M.D.¹

¹Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

²Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt

³School of Medicine, The University of Texas Health Science Center at Houston, McGovern School of Medicine, Houston, TX, USA

⁴School of Medicine, Texas Tech University Health Sciences Center, Paul L. Foster School of Medicine, El Paso, TX, USA

⁵Department of Radiation Oncology, The University of Texas Medical Branch, Galveston, Texas

⁶Department of Pathology, Division of Pathology/Lab Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

⁷Department of Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding authors: David I. Rosenthal, M.D. Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA. Telephone (713) 563-2353; Fax (713) 563-2366; dirosenthal@mdanderson.org & Abdallah S. R. Mohamed, M.D, MSc. Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA. Telephone (713) 745-4092; Fax (713) 563-2366; ASMohamed@mdanderson.org.

Authors who are responsible for statistical analyses: Clifton D. Fuller, Mona Kamal and Abdallah S. R. Mohamed. Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA. Telephone (713) 745-4092; Fax (713) 563-2366; CDFuller@mdanderson.org, MKJomaa@mdanderson.org and ASMohamed@mdanderson.org.

Conflict of Interest Disclosures:

All authors declare no conflict of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

⁸Department of Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

⁹Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

¹⁰Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, USA

¹¹Medical Physics Program, The University of Texas Graduate School of Biomedical Sciences, Houston, TX, USA

¹²Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

Abstract

Objectives—To investigate the impact of 3-Dimensional (3D) tumor volume (TV) and extent of involvement of primary tumor on treatment outcomes in a large uniform cohort of T3 laryngeal carcinoma patients treated with nonsurgical laryngeal preservation strategies.

Materials and Methods—The pretreatment contrast-enhanced computed tomography images of 90 patients with T3 laryngeal carcinoma were reviewed. Primary gross tumor volume (GTVp) was delineated to calculate the 3D TV and define the extent of invasion. Cartilage and soft tissue involvement was coded. The extent of invasion was dichotomized into non/limited invasion versus multiple invasion extension (MIE), and was subsequently correlated with survival outcomes.

Results—The median TV was 6.6 cm³. Sixty-five patients had non/limited invasion, and 25 had MIE. Median follow-up for surviving patients was 52 months. The 5-year local control and overall survival rates for the whole cohort were 88% and 68%, respectively. There was no correlation between TV and survival outcomes. However, patients with non/limited invasion had better 5-year local control (LC) than those with MIE (95% vs 72%, $p=0.009$) but did not have a significantly higher rate of overall survival (OS) (74% vs 67%, $p=0.327$). In multivariate correlates of LC, MIE maintained statistical significance whereas baseline airway status showed a statistically significance trend with poor LC ($p=0.0087$ and 0.06 , respectively). Baseline good performance status was an independent predictor of improved OS ($p=0.03$) in multivariate analysis.

Conclusion—The extent of primary tumor invasion is an independent prognostic factor of LC of the disease after definitive radiotherapy in T3 larynx cancer.

Keywords

Radiation Therapy; Chemoradiotherapy; T3 Laryngeal Cancer; Tumor Volume; Laryngeal Preservation

Introduction

The concept of nonsurgical laryngeal preservation was demonstrated as an alternative to total laryngectomy (TL) for patients with locally advanced laryngeal cancer in the landmark “Department of Veterans Affairs (VA) Laryngeal Cancer Study” (VALCS) in 1991 [1].

While advocating a general role for nonsurgical therapy for advanced laryngeal cancer, the VA study did suggest that this approach was less successful for patients with the most advanced (but resectable) disease, since 56% of patients with T4 disease required salvage laryngectomy compared with 29% with smaller tumors. Subsequently, the Radiation Therapy Oncology Group (RTOG) conducted the 91-11 trial to refine the optimal nonsurgical approaches [2, 3], in which patients with T4 disease were excluded. These trials have led to increased use of radiotherapy (RT) and chemotherapy in the treatment of locally advanced laryngeal cancer [4].

Staging of laryngeal cancer is principally based on vocal cord mobility and sites of extension. It evolved from, and largely remains based on, clinical observations measuring disease extent and based on disease subsites within the larynx. Radiography has improved over the decades, and has contributed to defining sites of involvement for staging purposes. For example, paraglottic extension, which can be appreciated only on anatomic-based imaging, now upstages the disease to the T3 category. Tumor volume is not used in any head and neck sites. Rather tumor dimensions in cm are used for staging in oral cavity and oropharyngeal cancers. Thus, the current tumor staging system for laryngeal cancer has limitations as a 2-dimensional tool [5, 6].

Three-dimensional (3D) tumor volume (TV), using pretreatment computed tomography (CT), has been explored as an alternative quantitative prognostic parameter [7, 8]. Mancuso et al. [9] have shown that pre-radiotherapy 3D TV could be used as an image biomarker for local control in patients with larynx cancer. In the modern era, we have also shown, in a large-scale dataset of patients with T4a laryngeal squamous cell carcinoma (LSCC), that 3D measured primary TVs of $\geq 21 \text{ cm}^3$ were associated with significantly poorer outcomes compared with TVs $< 21 \text{ cm}^3$ [9].

To this end, we investigated the impact of 3D TV and extent of tumor invasion on the oncological and survival outcomes in a large-scale uniform cohort of T3 LSCC patients treated with non-surgical laryngeal preservation strategies.

Materials and Methods

Patients

The medical records of patients with T3 LSCC treated with definitive RT $\pm$ chemotherapy between 2002 to 2011, at The University of Texas, MD Anderson Cancer Center were reviewed, under an IRB-approved protocol. Patients were staged according to the seventh edition of American Joint Committee on Cancer (AJCC) manual staging system [10]. The inclusion criteria were as follows:

1. Pathologic confirmation of LSCC
2. T3, N0-3, M0 disease
3. Availability of pre-treatment contrast-enhanced CT scans
4. Curative intent treatment with non-surgical larynx preservation approaches.

The medical records of all patients were reviewed to collect patients' demographic, clinical, radiologic, pathologic, and treatment data.

Imaging

All available pretreatment contrast-enhanced computed tomography (CECTs) of the head and neck for the cohort were reviewed. The pretreatment CECT was a reconstruction of 1- to 5-mm-thick contiguous sections, (only 6 patients had CT scans in 5mm slices), field of view (FOV) = 12–18 cm, a 512 × 512-mm matrix, and the plane of section parallel to the true vocal cords. Pretreatment CECT images were imported into commercial image segmentation software (Velocity AI v.3.01, Varian Medical Systems, Atlanta, GA).

Tumor Volume and Pattern of Invasion

Two measures of disease extent were determined and analyzed: TV, and extent of invasion. To determine the TV, the primary lesion was manually delineated on each CT slice that contained tumor by two co-authors (SAE, CDR), who were blinded to patient outcomes, and reviewed independently by two radiation oncologists (ASRM, MK). For quality assurance, a board-certified neuroradiologist with 7 years of H&N imaging experience (JMJ) validated a random set of images and reported that there were no significant discrepancies on the delineation (judged as changes ± 2 mm).

The extent of invasion was dichotomized into a non/limited invasion pattern or multiple invasion pattern based on our data for T4a larynx cancer [11]. Primary tumor abutting anatomical barriers, namely any combination of cartilage (arytenoid, cricoid, or inner cortex of thyroid) or soft tissue (post-cricoid, pyriform sinus, and pre-epiglottic space), were coded as invaded. Areas of tumor invasion were then categorized by number of structures involved, such as single cartilage or soft tissue versus multiple (e.g., inner thyroid cortex and pre-epiglottic space), and then grouped into a binary variable of non/limited invasion pattern or multiple invasion pattern (Figure 1).

Statistical Analysis

Spearman's rank correlation test was used to assess the correlation between TV and patterns of invasion. Log-rank test was used to compare univariate survival curves. Univariate and multivariate Cox proportional hazards assessments were performed to investigate the impact of the following variables with disease control and/or survival end points: age (≥ 60 versus <60 years), ethnicity (white versus non-white), sex, baseline ECOG (0–1 versus 2–3), subsite (glottic versus supraglottic), nodal stage (N0 versus N+), and receipt of concurrent chemotherapy (CCRT) (yes versus no). Cox proportional hazard models were used to investigate the impact of TV, pattern of invasion, and baseline functional status (i.e., vocal cord mobility and airway preservation) on the oncological outcomes.

The Kaplan-Meier method was used to calculate the survival end points. This analysis included local control (LC) and loco-regional control (LRC) defined as complete and continuous freedom from recurrence at the primary site, and at primary site and neck, respectively. Distant metastases-free survival (DMFS), recurrence-free survival (RFS, defined as time without recurrence, all others censored), progression-free survival (PFS,

defined as time free of cancer, with recurrence and death coded as events, all others censored), and disease-specific survival (DSS, defined as time alive free of cancer, with death from disease coded as an event, all others censored) were also computed. Composite functional/mortality end points were calculated for patients who had larynx preservation and for those with laryngo-esophageal dysfunction (LED)-free survival (LEDFS, with any death, local, relapse, salvage total laryngectomy, tracheotomy, and/or feeding tube placement/persistence recorded after 2 years coded as an event, censoring others). The end date of RT was used as a start time for survival analysis.

All analyses were performed using JMP Pro statistical software version 11.2.0 (SAS Institute Inc, Cary, NC). P-values less than 0.05 were deemed statistically significant in this hypothesis-generating dataset, and annotated with a “*”.

Results

Patient and Treatment Characteristics

Ninety patients were eligible for analysis. The median age at the time of initial diagnosis was 61.4 (range, 42 – 88.4) years. Seventy-three patients (81%) were males. The majority of tumors (61%) were of supraglottic origin. On histopathology, 8 (9%) were well differentiated (G1), with 39 (43%) and 24 (27%), being moderately (G2) and poorly (G3) differentiated, respectively.

All patients were treated with larynx preservation approaches (i.e., curative intent radiotherapy ± chemotherapy). Twenty-eight patients had induction chemotherapy, which consisted of taxane and/or platinum-based chemotherapy. Cetuximab was included in the induction regimen of four patients. A total of 78 patients received concurrent chemotherapy (CCRT); 55 received platinum single-agent chemotherapy, 6 patients received taxanes and platinum-based chemotherapy, and 16 patients received Cetuximab. As regards radiotherapy delivery, 34 patients (38%) received 2D/3D conformal RT, and 56 patients (62%) received IMRT, with median overall RT time of 44 days. Sixty-six patients were treated by conventional fractionation, and 24 with altered fractionation RT. Only 8 patients were treated by definitive RT alone; three due to poor tolerance to treatment, two diagnosed with very early glotticT3N0 (i.e. volume less 3.3 cm³, two patients presented poor performance status (ECOG 2–3), and one 88 years old with multiple comorbidities. Table 1 summarizes patients, disease and treatment characteristics.

Tumor Volume and Extent of Invasion Distribution

The median and interquartile range (IQR) TV for the entire cohort was 6.6 (4.6–11.7) cm³. TV and pattern of invasion showed weak correlation ($\rho=0.2$). The mean $\pm$ SD TV was 8.42 $\pm$ 5.1 versus 9.7 $\pm$ 7.4 cm³ across patients with non/limited versus multiple invasion extension (MIE) ($p=0.044$). A statistically significant difference was observed in TV between glottic and supraglottic tumors ($p<0.001$). The mean $\pm$ SD TV for glottic tumors was 4.9 $\pm$ 3.3 cm³, and supraglottic tumors was 11.1 $\pm$ 7.5 cm³. The vast majority of patients in this cohort (92%) had tumor volumes less than 21 cm³.

A total of 65 (72%) patients had either no invasion of the adjacent structures (n= 30) or limited invasion of only one structure (n= 35). Twenty-five patients (28%) had invasion of multiple adjacent structures. There was no statistically significant difference between pattern of invasion among patients with glottic/subglottic and supraglottic disease (p=0.89). Of the 25 patients with MIE, 15 had supraglottic and 10 had glottic/subglottic disease. Three of the 65 patients with non/limited invasion and 6 of the 25 with MIE developed local recurrence. Of those 25 patients; 13 patients had two sites of invasion and 12 patients had three sites of invasion. No patient had more than three sites involved. Out of the thirteen patients presenting with two sites of invasion, only one had LRF, he was eligible for salvage surgery. Among the 12 patients with three sites of invasion, five had LRF. Four of those five patients had salvage surgery for LRF, in which salvage was successful in 3 patients. The rate of tracheotomy at last follow-up was higher in patients with MIE (24 %) than in those with non/limited invasion (12%) (Supplementary Table 1).

Correlates of Survival Outcomes

Median follow-up for surviving patients was 52 (range, 3.6–134.3) months. Overall, 36 patients died; 11 from cancer-related causes and 25 from other causes. The 5-year actuarial LEDFS and OS rate was 57% (95% CI 45%-68%) and 68% (95% CI 56%-78%), respectively (Figure 2). On multivariate analysis, good ECOG status (ECOG 1–2) was an independent predictor of improved OS (HR 2.9; 95% CI 1.1–6.9, p=0.03) (Table 2). The 5-year OS of patients with MIE was numerically inferior compared with patients with non/limited invasion (67% vs 74%, respectively) (p=0.34). However, larger tumor volume (tested as a continuous variable) was not associated with worse survival (p=0.1).

Regarding the impact of baseline laryngeal functional status on clinical outcomes, patients with tracheotomy had worse 5-year survival (60%) than patients who did not require tracheotomy at presentation (70%)(p=0.018). However, after adjustment of the clinical variable, the need for tracheotomy at baseline did not affect OS (p=0.1) in multivariate analysis. The degree of vocal cord mobility was not correlated with OS in the univariate analysis. Patients with non/limited invasion had better 5-year LEDFS compared with patients with MIE (62% vs 47%, respectively; p=0.0816).

Correlates of Disease Recurrence

At last follow-up, 14 patients had disease recurrence. Sites of recurrence were local, 9, regional, 11, and distant, 5. 5-year LC, LRC, RFS, and FDM rates were 88% (95% CI 78%–94%), 85% (95% CI 75%–92%), 81% (95% CI 71%–88%), and 94% (95% CI 86%–97%), respectively. Of the 11 patients who had LRF; 6 were treated by salvage treatment, in which salvage was successful in only 2, with a median cancer free duration of 14 months after salvage treatment. Five-year ultimate LRC was 88%. Out of the 9 local failures; two were basically treated by 2D/3D and 7 by IMRT. 5-year LC was 94% vs. 82% after 2D/3D RT vs IMRT respectively, p= 0.22. Eight and three patients had LRF after IMRT and 2D/3D RT respectively. 5-year ultimate LRC was non-significantly poor in patients who were treated with IMRT compared to those who were treated with 2D/3D RT (85% compared to 91%, P=0.2). Univariate analysis revealed that tracheotomy at presentation and pattern of invasion were significantly correlated with the LC (p=0.11 and p=0.14, respectively).

Patients with MIE had significantly worse 5-year local control than those with non/limited invasion (72% vs 95%, $p=0.009$). Local control was poor in patients who presented with multiple invasion, although 92% of those patients received intensified treatment (i.e., CCRT $\pm$ IC). Post hoc analysis revealed that even after CCRT, 5-year LC was still poor in patients with multiple invasion compared with patients with limited invasion (74% vs. 96%, $p=0.017$). 5-year LC was 92% vs 55% in patients presented with two vs three sites of invasion respectively, $p=0.099$. In term of LRC, 5-year LRC was poor in patients presented with three sites of invasion compared to those who had two sites of invasion (47% compared to 92% respectively, $P=0.045$). Ultimate 5-year LRC was 92% and 57% in patients presented with two vs three sites of invasion respectively, $P=0.069$.

Five-year LC was better in patients with intact airway than in patients with tracheotomy at presentation (92% vs 66 %, respectively; $p=0.008$). However, TV was not statistically associated with poor LC ($p=0.184$). The degree of vocal cord mobility (i.e., impaired/paralysis vs. mobile) did not significantly affect the 5-year LC ($p=0.12$). After adjustment of the clinical variables, MIE maintained statistical significance in multivariate correlates of LC (HR 10.6; 95% CI 2.82–11.88), $p=0.0087$, and compromised airway (i.e., required tracheotomy) at presentation showed significant trend with poor LC ($p=0.06$).

Patients with non/limited invasion also had better 5-year PFS ($p=0.016$), and RFS compared with patients with MIE ($p=0.0029$) (Fig 3).

Discussion

Our study has demonstrated that the extent of invasion of the primary tumor was a significant independent prognostic factor for local control after definitive radiotherapy in patients with T3 laryngeal cancer, but it did not affect survival. The primary tumor volume and degree of vocal cord mobility did not correlate with clinical outcomes in T3 laryngeal cancer. Moreover, impaired airway at presentation requiring tracheotomy led to poor LC and OS in the univariate analysis. We also found that good performance status was the only independent predictor for better OS.

Since the VA larynx preservation trial was reported more than 3 decades ago, many patients with T3 laryngeal cancer have been treated with radiotherapy and chemotherapy (i.e., IC/RT only or CCRT) approaches. This has been an overall successful strategy, and our cohort of patients with T3 larynx cancer treated with nonsurgical larynx preservation approaches had overall better functional and oncological outcomes compared with historical cohorts who had total laryngectomy and post-operative radiotherapy (PORT), or RT alone [12].

However, even within a relatively narrow stage definition, T3 tumors are a heterogeneous group, and not all patients with T3 tumors are suitable for an organ preservation approach. Therefore, we undertook this study to determine whether measures of disease extent on radiographic (CT-based) imaging can help better select patients for laryngeal preservation.

We found that the invasive pattern of the tumor and invasion of anatomical barriers defined as MIE seem to be more important drivers for poor local control (5 year LC of 72% vs 95%). A pathology study by Serrano et al. [13] examined the patterns and degree of

laryngeal cartilage invasion in laryngectomy specimens and demonstrated that partial focal infiltration was identified in 27% of cases with thyroid cartilage invasion and in 53% of those with cricoid cartilage invasion. Moreover, the prognostic significance of degree and pattern of local cartilage(s) invasion has been echoed in several surgical studies [14, 15]. One further investigation is required to determine whether patients with invasion of multiple adjacent structures should be considered for multimodality treatment escalation. However, careful consideration of treatment modalities and dose escalation is required to maximize the therapeutic ratio; improving treatment outcomes while limiting treatment-related toxicity.

Several studies had evaluated the prognostic value of pre-treatment primary tumor volume, using older and less accurate imaging and treatment techniques in laryngeal cancer (Supplementary Table 2). The volumetric component could be used as an image biomarker in all stages and the original thought was it would serve as valid biomarker in all stages. As a whole, a larger tumor volume as a continuous measure conferred poorer prognosis in terms of local control [16–27] and OS [21, 23–26, 28]. However, when we tested this hypothesis in this dataset of exclusively T3 laryngeal cancer patients, the results showed that 3D volume did not actually correlate with outcomes and other factors like the nature of invasion was more prognostic than volume in this cohort. We think that the correlation of tumor volume with outcomes in prior papers may be due to the fact that most of these publications reported the entire spectrum of laryngeal cancer, rather than focusing on T3 tumors as in the present study. The majority of previous studies included a widely heterogeneous group of patients with different primary tumor (T) stages [18, 22, 27]. Studies that limited their cohorts to patients with T3 laryngeal cancer were small and were conducted in the pre-2000 era [16, 17]. We do recommend 2 mm for better image quality and minimize the operator-dependent errors in the head and neck [29]

Recent studies have proposed the TV threshold theory whereby a larger TV is associated with poorer outcomes. This correlates with the gradations of disease burden [25] and the tumor carrying capacity theories [30], which emphasize that treatment outcomes worsen after a specific TV threshold in which anatomical barriers are invaded. Such proposed theories could explain the findings of our recent article on patients with T4a laryngeal tumor which, identified pre-treatment TV $\geq 21\text{cm}^3$ as a driver for worse clinical outcome after definitive radiotherapy than those with TV $< 21\text{cm}^3$. Moreover, these same theories can explain our current observations, which show that the TV did not emerge as a significant prognostic factor in patients with T3 laryngeal tumor. The vast majority of patients in this cohort (92%) had tumor volumes less than 21cm^3 . Therefore, the substratification of patients according to the previously identified volume cutoff threshold in our prior paper does not apply in this cohort of rather smaller T3 tumor volume. Instead we found that patients with MIE not only had poorer tumor control, but this also had higher tracheotomy rates at presentation and last follow-up. For this reason, we heavily advocate that direct CT volumetric measurement be matched with expert radiologic assessment of extent of disease (ideally by a dedicated head and neck neuroradiologist, as in our center) in addition to clinical assessment of extension by endoscopic and clinical examination by a fellowship-trained head and neck specialist. In addition, we recommend functional assessment by a speech pathologist (including MBS and video-laryngoscopy) and primary assessment by head and neck radiation oncologists for better treatment selection.

This study comes with all the caveats of a single-institution retrospective study. Observed heterogeneous treatment approaches might introduce occult bias. Additionally, despite our best efforts to reduce inter-observer delineation variability by having two observers contour each case and two radiation oncologists checking the contour for clinical quality assurance, our study inherently is subjected to volumetric measurement variability. Some of the diagnostic CT scans utilized 5 mm slices, which might have failed to capture exceedingly limited TV extension. Nevertheless, our patients' overall clinical outcomes (LC, RFS, and OS) were as good or better [12] than those in similar cohorts [2, 31, 32].

After careful pre-treatment functional assessment and input from a multidisciplinary team, non-surgical laryngeal preservation for T3 cancers remains an excellent standard of care for appropriately selected patients. Based on our finding of poorer LC with MIE, we recommend that the pattern of invasion of the primary should be taken into consideration along with the above-mentioned functional assessments when selecting patients for laryngeal preservation. Patients with T3 laryngeal cancer with multiple invasion who wish to proceed with nonsurgical laryngeal preservation treatment may be counselled about the increased risks and consequences of local failure in order to set proper expectations and agree to more close surveillance to optimize surgical salvage treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant or financial support: Drs. Lai, Hutcheson, Mohamed and Fuller received funding support from the National Institutes of Health (NIH)/National Institute for Dental and Craniofacial Research (1R01DE025248-01/R56DE025248-01). Dr. Hutcheson and Fuller are supported via the NIH/National Cancer Institute (NCI) Small Grants Program for Cancer Research (R03 CA188162). Dr. Fuller is an MD Anderson Cancer Center Andrew Sabin Family Fellow, and received project support in this role from the Andrew Sabin Family Foundation. Dr. Fuller and Mohamed receive funding and/or salary support from the National Institutes of Health (NIH), including: a Big Data to Knowledge (BD2K) Program of the National Cancer Institute (NCI) Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science Award (1R01CA214825-01); NCI Early Phase Clinical Trials in Imaging and Image-Guided Interventions Program (1R01CA218148-01); an NIH/NCI Cancer Center Support Grant (CCSG) Pilot Research Program Award from the UT MD Anderson CCSG Radiation Oncology and Cancer Imaging Program (P30CA016672) and an NIH/NCI Head and Neck Specialized Programs of Research Excellence (SPORE) Developmental Research Program Award (P50 CA097007-10). Dr. Fuller has received direct industry grant funding and speaker travel from Elekta AB for unrelated technical projects. Family of Paul W. Beach is providing direct salary support for Dr. Kamal. Dr. Ng received grant funding from the Royal Australian and New Zealand College of Radiologists (RANZCR) and Radiological Society of North America (RSNA). These entities played no role in designing the study; collecting, analyzing, or interpreting its data; writing the manuscript; or making the decision to submit the report for publication.

References

1. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*. 1991; 324:1685–90. [PubMed: 2034244]
2. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *The New England journal of medicine*. 2003; 349:2091–8. [PubMed: 14645636]

3. Maor MH, Berkey B, Forastiere A, Weber R, Goepfert H, Morrison W, et al. Larynx preservation and tumor control in stage III and IV laryngeal cancer: a three-arm randomized intergroup trial; RTOG 91-11. *International Journal of Radiation Oncology*Biophysics*. 2002; 54:2-3.
4. Hoffman HT, Porter K, Karnell LH, Cooper JS, Weber RS, Langer CJ, et al. Laryngeal Cancer in the United States: Changes in Demographics, Patterns of Care, and Survival. *The Laryngoscope*. 2006; 116:1-13.
5. Harrison DF. Classification: the great deception. *The Journal of otolaryngology*. 1988; 17:12-5. [PubMed: 3343713]
6. Bailey BJ. Beyond the 'new' TNM classification. *Arch Otolaryngol Head Neck Surg*. 1991; 117:369-70. discussion 71. [PubMed: 2007005]
7. van den Broek GB, Rasch CR, Pameijer FA, Peter E, van den Brekel MW, Tan IB, et al. Pretreatment probability model for predicting outcome after intraarterial chemoradiation for advanced head and neck carcinoma. *Cancer*. 2004; 101:1809-17. [PubMed: 15386309]
8. Kneijens JL, Hauptmann M, Pameijer FA, Balm AJ, Hoebbers FJ, de Bois JA, et al. Tumor volume as prognostic factor in chemoradiation for advanced head and neck cancer. *Head Neck*. 2011; 33:375-82. [PubMed: 20629076]
9. Shiao JC, Mohamed ASR, Messer JA, Hutcheson KA, Johnson JM, Enderling H, et al. Quantitative pretreatment CT volumetry: Association with oncologic outcomes in patients with T4a squamous carcinoma of the larynx. *Head & Neck*. 2017; 39:1609-20. [PubMed: 28464542]
10. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. *Annals of Surgical Oncology*. 2010; 17:1471-4. [PubMed: 20180029]
11. Mohamed ASR, Pham BH, Messer JA, Morrison WH, Zafereo M, Hessel AC, et al. Identification of Anatomic Correlates of Failure in Patients With T4a Larynx Cancer. *International Journal of Radiation Oncology*Biophysics*. 2016; 94:896.
12. Fuller CD, Mohamed ASR, Garden AS, Gunn GB, Mulcahy CF, Zafereo M, et al. Long-term outcomes after multidisciplinary management of T3 laryngeal squamous cell carcinomas: Improved functional outcomes and survival with modern therapeutic approaches. *Head & Neck*. 2016; 38:1739-51. [PubMed: 27466789]
13. Gómez Serrano M, Iglesias Moreno MC, Gimeno Hernández J, Ortega Medina L, Martín Villares C, Poch Broto J. Cartilage invasion patterns in laryngeal cancer. *European Archives of Oto-Rhino-Laryngology*. 2016; 273:1863-9. [PubMed: 26100029]
14. Fagan JJ, D'Amico F, Wagner RL, Johnson JT. Implications of cartilage invasion in surgically treated laryngeal carcinoma. *Head Neck*. 1998; 20:189-92. [PubMed: 9570622]
15. Yilmaz T, Hosal AS, Gedikoglu G, Kaya S. Prognostic significance of histopathological parameters in cancer of the larynx. *Eur Arch Otorhinolaryngol*. 1999; 256:139-44. [PubMed: 10234483]
16. Lee WR, Mancuso AA, Saleh EM, Mendenhall WM, Parsons JT, Million RR. Can pretreatment computed tomography findings predict local control in T3 squamous cell carcinoma of the glottic larynx treated with radiotherapy alone? *Int J Radiat Oncol Biol Phys*. 1993; 25:683-7. [PubMed: 8454487]
17. Pameijer FA, Mancuso AA, Mendenhall WM, Parsons JT, Kubilis PS. Can pretreatment computed tomography predict local control in T3 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy? *Int J Radiat Oncol Biol Phys*. 1997; 37:1011-21. [PubMed: 9169807]
18. Mukherji SK, O'Brien SM, Gerstle RJ, Weissler M, Shockley W, Castillo M. Tumor volume: an independent predictor of outcome for laryngeal cancer. *J Comput Assist Tomogr*. 1999; 23:50-4. [PubMed: 10050807]
19. Mukherji SK, O'Brien SM, Gerstle RJ, Weissler M, Shockley W, Stone JA, et al. The ability of tumor volume to predict local control in surgically treated squamous cell carcinoma of the supraglottic larynx. *Head Neck*. 2000; 22:282-7. [PubMed: 10748452]
20. Hermans R. Staging of laryngeal and hypopharyngeal cancer: value of imaging studies. *Eur Radiol*. 2006; 16:2386-400. [PubMed: 16733680]

21. Doweck I, Denys D, Robbins KT. Tumor volume predicts outcome for advanced head and neck cancer treated with targeted chemoradiotherapy. *Laryngoscope*. 2002; 112:1742–9. [PubMed: 12368607]
22. Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Mancuso AA. Parameters that predict local control after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Head Neck*. 2003; 25:535–42. [PubMed: 12808656]
23. van Bockel LW, Monninkhof EM, Pameijer FA, Terhaard CH. Importance of tumor volume in supraglottic and glottic laryngeal carcinoma. *Strahlenther Onkol*. 2013; 189:1009–14. [PubMed: 24196282]
24. Yang CJ, Kim DY, Lee JH, Roh JL, Choi SH, Nam SY, et al. Prognostic value of total tumor volume in advanced-stage laryngeal and hypopharyngeal carcinoma. *J Surg Oncol*. 2013; 108:509–15. [PubMed: 24590673]
25. Hsin LJ, Fang TJ, Tsang NM, Chin SC, Yen TC, Li HY, et al. Tumor volumetry as a prognostic factor in the management of T4a laryngeal cancer. *Laryngoscope*. 2014; 124:1134–40. [PubMed: 24127228]
26. Yabuki K, Shiono O, Komatsu M, Sano D, Nishimura G, Takahashi M, et al. Predictive and prognostic value of metabolic tumor volume (MTV) in patients with laryngeal carcinoma treated by radiotherapy (RT)/concurrent chemoradiotherapy (CCRT). *PLoS One*. 2015; 10:e0117924. [PubMed: 25692986]
27. Timmermans AJ, van Dijk BA, Overbeek LI, van Velthuysen ML, van Tinteren H, Hilgers FJ, et al. Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands. *Head Neck*. 2016; 38(Suppl 1):E1247–55. [PubMed: 26315454]
28. Strongin A, Yovino S, Taylor R, Wolf J, Cullen K, Zimrin A, et al. Primary tumor volume is an important predictor of clinical outcomes among patients with locally advanced squamous cell cancer of the head and neck treated with definitive chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2012; 82:1823–30. [PubMed: 21549516]
29. Sturgeon JD, Cox JA, Mayo LL, Gunn GB, Zhang L, Balter PA, et al. Improved human observer performance in digital reconstructed radiograph verification in head and neck cancer radiotherapy. *International journal of computer assisted radiology and surgery*. 2015; 10:1667–73. [PubMed: 25477277]
30. Enderling H, Chaplain MA. Mathematical modeling of tumor growth and treatment. *Curr Pharm Des*. 2014; 20:4934–40. [PubMed: 24283955]
31. Dziegielewski PT, O'Connell DA, Klein M, Fung C, Singh P, Alex Mlynarek M, et al. Primary total laryngectomy versus organ preservation for T3/T4a laryngeal cancer: a population-based analysis of survival. *J Otolaryngol Head Neck Surg*. 2012; 41(Suppl 1):S56–64. [PubMed: 22569051]
32. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol*. 2011; 100:33–40. [PubMed: 21684027]
33. Lo SM, Venkatesan V, Matthews TW, Rogers J. Tumour volume: implications in T2/T3 glottic/supraglottic squamous cell carcinoma. *J Otolaryngol*. 1998; 27:247–51. [PubMed: 9800621]
34. Mancuso AA, Mukherji SK, Schmalfuss I, Mendenhall W, Parsons J, Pameijer F, et al. Preradiotherapy computed tomography as a predictor of local control in supraglottic carcinoma. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 1999; 17:631–7. [PubMed: 10080608]
35. Hermans R, Van den Bogaert W, Rijnders A, Baert AL. Value of computed tomography as outcome predictor of supraglottic squamous cell carcinoma treated by definitive radiation therapy. *Int J Radiat Oncol Biol Phys*. 1999; 44:755–65. [PubMed: 10386632]
36. Hoebbers FJ, Pameijer FA, de Bois J, Heemsbergen W, Balm AJ, Schornagel JH, et al. Prognostic value of primary tumor volume after concurrent chemoradiation with daily low-dose cisplatin for advanced-stage head and neck carcinoma. *Head Neck*. 2008; 30:1216–23. [PubMed: 18642295]
37. Kats SS, Muller S, Aiken A, Hudgins PA, Wadsworth JT, Shin DM, et al. Laryngeal tumor volume as a predictor for thyroid cartilage penetration. *Head Neck*. 2013; 35:426–30. [PubMed: 22488941]

38. Janssens GO, van Bockel LW, Doornaert PA, Bijl HP, van den Ende P, de Jong MA, et al. Computed tomography-based tumour volume as a predictor of outcome in laryngeal cancer: results of the phase 3 ARCON trial. *Eur J Cancer*. 2014; 50:1112–9. [PubMed: 24424106]
39. Hurst NJ Jr, Pereira LM, Dominello MM, Dyson G, Laszewski P, Robinette N, et al. Pretreatment computed tomographic gross tumor volume as predictor of persistence of tracheostomy and percutaneous endoscopic gastrostomy tube in patients undergoing larynx preservation. *Head Neck*. 2016; 38:1455–8. [PubMed: 27131223]

Research Highlights

In T3 larynx cancer patients treated with non-surgical conservative approaches:

- The extent of invasion of the primary tumor is an independent prognostic factor of the local control.
- The primary tumor volume and degree of vocal cord mobility didn't correlate with patient outcomes.
- Impaired airway at presentation requiring tracheotomy led to poor local control and survival.
- Baseline good performance status is an independent predictor of improved overall survival.
- Patients with multiple invasion may be counselled about close surveillance.

Figure 1. Examples of Pretreatment Contrast Enhanced CT Images Showing Different Patterns of Invasion

A: The top image is for a patient with relatively large TV (i.e., 34.9 cm³), although the tumor showed no invasion. This patient was cancer-free after more than 2 years of follow-up.

B: The bottom image is for a patient with relatively small TV (i.e., 4.8 cm³); however, the tumor had MIE. The tumor showed invasion of the inner cortex of thyroid cartilage and pre-epiglottic space (right wing of the thyroid cartilage was cropped to show invasion). This patient had a LR recurrence after 5.7 months of follow-up and died 10 months later.

Figure 2. Kaplan-Meier Curve Plot of the Survival Outcomes for the Whole Cohort (n=90); Local Control (LC), Laryngo-Esophageal Dysfunction Free Survival (LEDFS), and Overall Survival (OS).

Figure 3. Kaplan-Meier Curve Plot of Survival and Oncological Outcomes According to the Extent of Invasion of Primary Tumor (Non/Limited Invasion [n = 65] and Multiple Invasion [n = 25]);
 Local Control (LC), Local Regional Control (LRC), Recurrence-Free Survival (RFS), Event-Free Survival (EFS), Laryngectomy Free Survival (LFS), Laryngo-Esophageal Dysfunction Free Survival (LEDFS), disease-specific survival (DSS), and Overall Survival (OS).

Table 1

Patient, disease, and treatment characteristics

Characteristic	No. (%) *
Sex	
Male	73 (81)
Female	17 (19)
Age (years)	
Median	61
Range	42–88
Ethnicity	
White	60 (67)
African American	12 (13)
Hispanic	12 (13)
Others	6 (7)
Primary Subsite Epicenter	
Glottis	34 (38)
Supraglottis	55 (61)
Subglottis	1 (1)
Lymph Node Status	
N0	47 (52)
N1	11 (12)
N2	31 (35)
N3	1 (1)
Smoking History	
Yes	85 (94)
No	5 (6)
Radiotherapy Technique	
2D/3D RT	34 (38)
IMRT	56 (62)
Mean Total Radiation Dose $\pm$ SD, Gy	70.2 $\pm$ 0.7
Mean Overall RT time $\pm$ SD	44 $\pm$ 3.95
Fractionation Schedule	
Conventional	66 (73)
Altered	
Twice Daily	1 (1)
Concomitant Boost	23 (26)
Chemotherapy	
Induction Chemotherapy + CCRT	24 (26.7)
CCRT	54 (60)

Characteristic	No. (%) [*]
Induction Chemotherapy Followed by RT	4 (4.3)
RT alone	8 (9)

Abbreviations: CCRT, Chemoradiotherapy; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

^{*} Unless otherwise indicated.

Table 2

Univariate and Multivariate Analysis of Correlates of Survival

Characteristic	Univariate OS Analysis		Multivariate OS Analysis	
	HR (95% CI)	p-value*	HR (95%CI)	p-value*
Age (Years)				
<60	1			
60	1.7 (0.88–3.71)	0.1143		
Ethnicity				
Non-white	1			
White	1.4 (0.72–2.8)	0.293		
Gender				
Male	1			
Female	1.49 (0.7–3)	0.32		
ECOG Status				
0–1	1		1	
2–3	3.32 (1.3–7.5)	0.0145**	2.9 (1.1–6.9)	0.03**
Subsite				
Glottic	1			
Supraglottic	1.37 (0.7–2.8)	0.2796		
Nodal Status				
N0	1			
N+	1.46 (0.72–2.9)	0.2878		
CCRT				
Yes	1		1	
No	2.37 (1.12–4.6)	0.0246**	1.5 (0.5–3.5)	0.396
Extent of Invasion				
Limited invasion	1			
MIE	1.4 (0.668–2.89)	0.3406		
Tumor Volume				
Continuous		0.997		
Tracheotomy at baseline				
No	1		1	
Yes	2.4 (1.07–5)	0.03**	1.4 (0.7–4.6)	0.18
Vocal cord mobility at baseline				
Normal/limited	1			
Paralyzed	1.7 (0.89–3.5)	0.09		

* P values were calculated by the Chi-square test.

** Significant P values. Abbreviations: CCRT, chemoradiotherapy; OS, overall survival.