Published in final edited form as:

JAMA Otolaryngol Head Neck Surg. 2017 April 01; 143(4): 355–366. doi:10.1001/jamaoto.2016.3669.

Survival Rates Using Individualized Bioselection Treatment Methods in Patients with Advanced Laryngeal Cancer : The University of Michigan Experience

Gregory T. Wolf, MD¹, Emily Bellile, MS⁴, Avraham Eisbruch, MD³, Susan Urba, MD², Carol R. Bradford, MD¹, Lisa Peterson, MS¹, Mark E. Prince, MD¹, Theodoros N. Teknos, MD⁵, Douglas B. Chepeha, MD⁶, Norman D. Hogikyan, MD¹, Scott A. McLean, MD¹, Jeffery Moyer, MD¹, Jeremy MG Taylor, PhD⁴, and Francis P. Worden, MD²

¹Department of Otolaryngology-Head and Neck Surgery, University of Michigan Health System, Ann Arbor, MI, 48109

²Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI, 48109

³Department of Radiation Oncology, University of Michigan Health System, Ann Arbor, MI, 48109

⁴Department of Biostatistics, University of Michigan Health System, Ann Arbor, MI, 48109

⁵Department of Otolaryngology-Head and Neck Surgery, The Ohio State University, Wexner Medical Center, Columbus, OH 43212

⁶Department of Otolaryngology, University of Toronto, Toronto, CA

Abstract

The introduction of chemoradiation for advanced laryngeal cancer led to a major paradigm shift in treatment as an alternative to laryngectomy. Despite widespread adoption, survival rates have not improved and the original premise of matching neoadjuvant chemotherapy tumor response to determine subsequent treatment has not been followed. A unique approach incorporating a single cycle of neoadjuvant chemotherapy to select patients with advanced disease for either laryngectomy or concurrent chemoradiation was studied to determine if improved survival could be achieved.

Design—From 2002–2012, we treated an unselected cohort of 247 patients with laryngeal cancer in an academic institution.

Interventions—Limited disease patients (n=94) underwent endoscopic resection (n=33; 35%), radiation (n=50; 53%) or chemoradiation for deeply invasive T2 lesions (n=11; 12%). For advanced disease (n=153), neoadjuvant chemotherapy for treatment selection (n=71; 46%), concurrent chemoradiation (n=50; 33%) or primary surgery (n=32; 21%) was recommended.

Corresponding author: Gregory T. Wolf, MD, Professor, Chair Emeritus, Department of Otolaryngology-Head and Neck Surgery, 1903 Taubman Bldg, Box 5312, University of Michigan Health System, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, gregwolf@med.umich.edu, Office: 734-936-9178.

Level of Evidence: 2b

Outcomes—Propensity for treatment selection in advanced patients was modeled using logistic regression. Overall (OS) and disease specific survival (DSS) were analyzed with Cox proportional hazards models stratified by propensity score. Median follow was 48 months.

Results—Five-year OS and DSS was 75% (95% C.I. 68–81%) and 83% (77–88%), respectively for the entire cohort. DSS was 92% (83–97%) for patients with Stage I, II and 78% (69–84%) for patients with Stage III, IV disease. For advanced disease patients, 5-year OS (and DSS) ranged from 78% (91%) for surgery to 76% (79%) for neoadjuvant bioselection and 61% (66%) for primary chemoradiation. Propensity-adjusted multivariable Cox models controlling for known prognostic factors showed DSS was significantly improved in the neoadjuvant group compared to definitive chemoradiation [Hazard ratio 0.48, 95% CI: (0.29, 0.80), $p=0.005$]. DSS for the definitive surgery group was significantly better compared to the neoadjuvant bioselection group, [Hazard ratio 0.34, 95% CI: (0.14, 0.82), $p=0.02$]. Larynx preservation was achieved in 65% of advanced patients.

Conclusions—Exceptional survival rates were achieved with a bioselective treatment approach utilizing a single cycle of neoadjuvant chemotherapy. Excellent survival rates were also achieved in patients selected for primary surgery and both were better than with concurrent chemoradiation suggesting that the optimal individualized treatment approach for patients with advanced laryngeal cancer has not yet been defined.

Keywords

Laryngeal cancer; organ preservation; chemoradiation; neoadjuvant

Introduction

Over the past 30 years, survival rates for laryngeal cancer patients have not improved and some investigators have raised concerns that 5 year Surveillance, Epidemiology and End Results Program (SEER) survival rates for patients with advanced cancer have actually declined with the introduction of chemotherapy and radiation treatment strategies for organ preservation^{1–3}. Disease specific survival rates for limited cancers (Stages I, II) typically range from 60–90% while the best reported rates for patients with advanced cancers (Stages III, IV) only range from 50–60%^{4–6}. For patients with limited disease, laser assisted endoscopic resection as an alternative to definitive radiation or hemilaryngectomy has been widely adopted for patients with Stage I, II and selected Stage III patients^{7,8}. However, the optimal treatment approach for patients with advanced laryngeal cancer who face total laryngectomy remains unclear and controversy exists in recommending a primary surgical versus non-surgical approach^{6,9–13}.

For patients with advanced disease, the Department of Veteran's Affairs (VA) initiated the first randomized trial comparing a standard surgical approach (total laryngectomy) to an innovative approach that incorporated neoadjuvant chemotherapy followed by definitive radiation¹⁴. Integrated into this experimental strategy was early laryngectomy for patients who were non-responders after multiple cycles of neoadjuvant chemotherapy. Although the results of the VA trial failed to demonstrate a survival advantage for the experimental treatment regimen, two thirds of the patients were able to avoid laryngectomy without any

significant decrease in survival or quality of life compared to patients randomized to total laryngectomy^{14,15}. Two subsequent randomized trials testing the VA trial approach confirmed these results^{16,17} and showed that the highest larynx preservation rates were achieved with concurrent chemoradiation compared to a sequential neoadjuvant approach or to radiation alone¹⁷. Large meta-analyses have documented better survival with combinations of chemotherapy and radiation over radiation alone¹⁸ and better results for concurrent chemoradiation compared to neoadjuvant¹⁹. However more recent randomized trials fail to show improvements in survival comparing various intensive neoadjuvant versus sequential or concurrent chemoradiation approaches^{20–22}. Based on these cumulative experiences, a standard treatment approach of concurrent chemoradiation has been widely adopted as the preferred alternative to total laryngectomy for patients with advanced laryngeal cancer who are seeking larynx preservation²³. Unfortunately, 5 year overall survival rates remain less than 50%^{4,24}. Since survival rates in trials with concurrent chemoradiation have not improved while toxicities are increased, concerns have been raised about the wisdom of potentially preserving a non-functional larynx especially in cases of patients with T4a cancers where significant dysfunction and long term aspiration could be a potential problem. In fact, T4a cancers are often considered a contraindication for chemoradiation¹⁰. Because of these various results, neoadjuvant chemotherapy strategies to select patients for organ preservation have remained an investigative option²⁵.

Largely ignored in the past development of organ preservation treatment strategies has been the evidence that cancers showing a rapid response to neoadjuvant chemotherapy have a favorable response to subsequent radiation and improved survival²⁶. In fact, the most consistent observation in all trials of neoadjuvant chemotherapy has been the association of tumor response to chemotherapy and favorable prognosis. To further test the concept of using a response to chemotherapy as a basis to individualize therapy for Stage III, IV patients who face total laryngectomy, we conducted a series of Phase II trials using a single cycle of cisplatin-based neoadjuvant chemotherapy to select patients for subsequent radiation therapy^{26–28}. Responders (>50% primary tumor reduction) went on to a definitive course of chemoradiation (concurrent cisplatin) and non-responders underwent immediate total laryngectomy followed by adjuvant radiation. The results unexpectedly demonstrated extraordinarily high 5 year disease specific survival (82%; 95% C.I.= 72% – 89%) for an unselected cohort of 97 very advanced disease patients (including T4a) that was superior to outcomes we had achieved in prior trials^{27,28}. The favorable survival was evident in both the group of responders selected for subsequent chemoradiation and the non-responder group undergoing surgical total laryngectomy. Typically, patients failing multi-cycle neoadjuvant chemotherapy show a poor rate of survival, thus these results were unexpected, exciting and demanded validation.

Following these trials, we adopted a standard institutional approach to patients with advanced laryngeal cancer that offered all patients an initial cycle of neoadjuvant therapy and then a definitive treatment decision as to total laryngectomy versus definitive chemoradiation based on the neoadjuvant chemotherapy response. For patients refusing chemotherapy or medically unfit, primary total laryngectomy was recommended. Some patients were offered primary concurrent chemoradiation or radiation alone if they refused

the possibility of selection for total laryngectomy or wanted exclusively non-surgical treatment.

To determine outcomes of these individualized treatment decision criteria, including bioselection with neoadjuvant chemotherapy, we performed a retrospective cohort analysis of overall and disease specific survival for all previously untreated laryngeal cancer patients seen at the University of Michigan from 2002–2012.

Methods

Patient Population and Treatment Regimens

From 2002 to 2012, two hundred ninety three cases of laryngeal cancer were evaluated and consented for enrollment in our Institutional Review Board approved prospective epidemiology project that assessed correlations between treatment outcomes and clinical, genetic and health behavior characteristics. A total of 46 (16%) patients were excluded from the current analysis because they were treated for palliation (n= 27), refused all treatment (n= 14), were previously treated (i.e. recurrent cancer) or were not squamous histology (n=5). This left a total of 247 evaluable cases consisting of 115 (47%) glottic and 132 (53%) supraglottic cancers (Table 1). Cohort clinical characteristics and treatments are shown in Table 1. Primary treatment regimen differed by tumor stage and included combination chemotherapy and radiation in 115 (47%), radiation alone in 56 (23%) and primary surgery +/- radiation in 76 (31%) patients. For patients with limited cancers not requiring total laryngectomy, treatment decisions were based on tumor extent and logistics and expected quality of voice. If tumors were superficial and endoscopically accessible, an endoscopic partial laryngectomy was recommended. For larger cancers, (e.g. T2) that might have significant functional disability with surgical resection, primary radiation, or in some instances, concurrent chemoradiation was proposed.

Of the 153 patients with advanced (Stage III, IV) disease, 71 (46%) received a single cycle of neoadjuvant chemotherapy (cisplatin/5-Fluorouracil or carboplatin) and partial tumor response was used to select patients for definitive chemoradiation (cisplatin 100 mg/m² or carboplatin AUC 6—if not candidates for cisplatin) and non-response was an indication for total laryngectomy. Tumor response was based on visible change in bi-dimensional primary tumor measures based on office or operating room endoscopy and supplemented by CT or MRI images when available. Change in estimated greatest dimension and its perpendicular was recorded as a percentage and patients with greater than 50% reduction were considered responders. The patients experienced expected toxicities associated with cisplatin or carboplatin and 5-fluorouracil chemotherapy. The majority of patients experienced Grade 1–2 toxicities. A small number experienced Grade 3–4 toxicities prompting hospitalization. The reasons for admission were febrile neutropenia—3 patients, acute dehydration related to Grade 3 mucositis—5 patients, and Grade 3 intractable nausea—4 patients. One patient experienced a Grade 5 toxicity related to liver failure after receiving 5-FU. Of all patients treated with radiation alone, 89% were Stage I/II which contrasts with chemoradiation where 90% of patients were Stage III, IV. For patients undergoing primary surgery, 49% were Stage I, II and 51% were Stage III, IV. Treatment according to T classification is shown in e-Table 1. Treatment selection criteria (e-Table 2) for patients with limited disease (Stage I, II)

included endoscopic resection (n= 33; 35%), radiation alone (N=50; 53%) or concurrent chemoradiation for deeply invasive T2 lesions (n=11; 12%). For patients with advanced disease (Stage III, IV), induction chemotherapy for treatment selection was used in 71, (46%). Concurrent chemoradiation (cisplatin 100 mg/m² or carboplatin AUC 6) was used for patients refusing neoadjuvant chemotherapy or for logistical issues in 50; (33%). Primary laryngectomy was used in 21% for severely compromised larynx (n=26) or for patients who were possible candidates for larynx preservation with a supraglottic laryngectomy (n=6) (Figure 1). All patients were discussed at a multidisciplinary tumor board prior to treatment recommendations and all patients were followed closely after treatment by our team for possible recurrence. Patients receiving chemoradiation at outside facilities had treatment plans reviewed and had follow up by our treatment team. All patients were seen weekly in our medical oncology and radiation oncology clinics during their treatments with chemoradiotherapy. Median follow up for all patients was 48 months.

Statistical Analysis

Overall (OS) and disease specific (DSS) survival times were defined from date of diagnosis to death or last follow up. Deaths from causes other than cancer were censored at date of death for DSS analysis. The Kaplan-Meier method was used to estimate OS and DSS rates with 95% confidence intervals of the point estimates using a log-log transformation. Multivariable analyses were carried out using Cox proportional hazards regression models within the limited (stage I, II) and advanced (stage III, IV) stage patients separately. In limited stage patients, we also performed Cox multivariable analyses excluding 9 patients with in situ carcinoma leaving 85 limited stage patients (25 surgery, 60 chemoradiation or radiation) and tested for differences in OS and DSS by treatment, controlling for Stage (I vs II) in the model.

Among the 153 Stage III, IV patients, patient and tumor characteristics differed between treatment approaches, we performed propensity score adjusted multivariable Cox model analyses for OS and DSS comparing the three treatment approaches. Two separate analyses were carried out comparing (1) neoadjuvant bioselection to definitive chemoradiation and (2) neoadjuvant bioselection to definitive surgery. Propensity scores were derived from a logistic regression model for the probability of neoadjuvant therapy compared to definitive chemoradiation (analysis 1) or definitive surgery (analysis 2). The final propensity models for neoadjuvant selection included age, gender, comorbidity, current smoking, tumor stage, disease subsite, and year of diagnosis and resulted in c-statistics of 0.76 and 0.72 for the chemoradiation comparison and surgery comparison, respectively. Propensity scores were used to create weighted datasets using inverse probability of treatment weighting (IPTW) and results for propensity weighted Cox regression models among the Stage III, IV patients are reported.²⁹ In addition, sensitivity analyses were performed using the propensity information in different ways. We performed a second weighted Cox model that trimmed extreme propensity weights (<0.2 or >5) and also Cox models that stratified the baseline hazard function by propensity scores grouped in quintiles. These sensitivity analyses yielded the same conclusions (though slightly different point estimates) as the reported IPTW Cox multivariable results (data not shown). All analyses were performed using SAS software, Version 9.4 (SAS Institute, Cary, NC) for Windows.

Results

Overall and Disease Specific Survival

Estimated 5 year OS for the combined cohort was 75% (95% C.I., 68–81) and ranged from 81% (95% C.I., 69–89) for Stages I, II to 72% (95% C.I., 63–79) for Stages III, IV. Estimated 5 year DSS for the entire cohort was 83% (95% C.I., 77–88) and for patients with Stage III, IV disease was 78% (95% C.I., 69–84) compared 92% (95% C.I., 83–97) for limited disease patients. Estimated five year OS and DSS for the advanced disease patients (Stage III, IV) treated with neoadjuvant bioselection was 76% (95% C.I., 63–85) and 79% (95% C.I., 67–88) respectively. There were no significant differences in OS according to glottic vs. supraglottic disease subsite or comparing Stage I, II to Stage III, IV. However, when pairwise comparisons by disease stage were performed by log-rank testing, results for Stage I compared to Stage IV differed significantly for disease specific survival but not for overall survival. All other comparisons failed to find statistically different survival rates for advanced disease patients compared to limited disease patients (Figure 2).

When all patients were combined, survival outcomes differed by treatment and favored primary surgery. Overall survival was similar for patients treated with radiation alone or chemoradiation and was significantly inferior to patients treated with primary surgery (Figure 3). The improved survival associated with primary surgery was due in part to results achieved for limited disease patients, where primary surgery resulted in excellent survival and 100% larynx preservation compared to radiation therapy. The surgery alone group benefited by inclusion of 9 patients who underwent endoscopic resections for carcinoma in situ.

Limited Laryngeal Cancer (Stage I, II) Treatment and Outcomes

Initial treatment for the 94 patients with limited cancers included surgery (n=33; 35%), radiation alone (n=50; 53%) or concurrent chemoradiation (n=11; 12%). Organ preservation was achieved in 94% of patients with none of the surgical patients requiring total laryngectomy while 5 (10%) radiation patients and 1 (8%) chemoradiation patient eventually required total laryngectomy. Five year OS for limited disease patients was significantly better for primary surgery compared to radiation/chemoradiation (97% vs 71%). The increase in OS survival proportion was 26% with 95% CI [4%, 48%]. There was a 7% difference in DSS 97% vs. 90% which did not reach statistical significance (95% C.I. of absolute difference [–17%, 31%] (Figure 4). The outcome differences were confounded by differences in patient characteristics such as T class. Surgically treated patients were significantly more likely to be lower stage. After excluding 9 patients with in situ carcinoma and controlling for stage in a multivariable Cox model, the survival advantage of surgery remained but was not statistically significant for either OS or DSS (HR =0.17 [0.02, 1.41] and HR =0.70 [0.07, 7.739] respectively).

Advanced Laryngeal Cancer (Stage III, IV) Treatment and Outcomes

Initial treatment for 153 advanced disease patients included primary surgery (n=32; 26 total laryngectomy and 6 supraglottic laryngectomy), neoadjuvant chemotherapy for treatment selection (n=71; 46%), or definitive concurrent chemoradiation (n=45; 29%) and radiation

alone (n=5; 3%) (Figure 1). The neoadjuvant bioselection group had 11 patients referred for total laryngectomy based on poor tumor response and 60 patients referred for definitive chemoradiation. A total of 13 additional laryngectomies were eventually required among the patients referred for chemoradiation after neoadjuvant selection and only 4 after definitive chemoradiation.

Overall 5 year survival was 72% (95% C.I. 63–79) for the entire cohort of advanced patients and varied from 76% (95% C.I. 63–85) for neoadjuvant bioselection treatment to 61% (95% C.I. 44–75) for the primary chemoradiation subgroup. Five year DSS was 78% (95% C.I. 69–84) for all advanced patients together, and varied from 91% (95% C.I. 67–98) for primary surgery to 79% (95% C.I. 67–88) for neoadjuvant bioselection and 66% (95% C.I. 48–79) for the chemoradiation subgroup. When comparing survival by planned initial treatment, no significant pairwise differences were noted in OS, but DSS was higher for primary surgery compared to chemoradiation (Figure 5). By Cox regression analysis, OS and DSS were significantly improved in the neoadjuvant group compared to definitive chemoradiation/radiation without induction selection [Hazard ratio 0.36, 95% CI: (0.16, 0.81), $p=0.01$) and HR 0.37, 95% CI: (0.16, 0.90), $P=0.03$, respectively] after controlling for age, stage (III vs IV), comorbidities, and current smoking, (eTables 3,4). Furthermore, OS and DSS for the neoadjuvant group were similar to the surgery group, [Hazard ratio 1.33, 95% CI: (0.46, 3.38), and 3.32, 95% CI: (0.70, 15.88), respectively] (eTables 5,6).

When patients with advanced disease were grouped by T classification, the majority (54%) of patients with T4a cancers were treated with neoadjuvant bioselection and most patients (52%) with T1 or T2 primaries underwent definitive chemoradiation. Only 17% of T3 cases and 27% of T4 cases went to primary surgery (e-Table 1). When analyzed by both tumor site and stage, it was evident that Stage IV patients were more likely to have neoadjuvant bioselection with equal proportions of glottic and supraglottic sites. However, for patients not receiving neoadjuvant bioselection, 9 of 12 (75%) Stage IV glottic patients went to primary surgery rather than chemoradiation. We found no significant differences in either OS or DSS for patients according to T class (T1,2 vs T3 vs T4a) by log rank testing with Tukey-Kramer adjustment for multiple comparisons (e-Figure 1). Finally, cause of death did not differ among the various treatment approaches. For the entire cohort of 247 patients 47 (19%) deaths were recorded with 30 (64%) due to recurrent malignancy, 10 (21%) from other non-cancer causes and 7 (15%) from unknown cause. For the 71 patients treated with neoadjuvant bioselection, there were 14 deaths; 12 of which were from cancer and 2 were from other causes.

Analysis of Neoadjuvant Bioselection in Advanced Disease Adjusted for Patient and Tumor Characteristics

Because treatment selection was non-random and subject to patient and physician preferences, we further explored differences in outcomes to determine if there was benefit from neoadjuvant bioselection compared to other treatments by performing a propensity score adjusted comparison to account for differences in patient and tumor characteristics that might have influenced treatment decisions. Among all 153 stage III, IV patients, two propensity score adjusted multivariable Cox model analyses were performed for DSS and

OS comparing neoadjuvant bioselection to definitive surgery and to definitive chemoradiation. The propensity score models were derived from a logistic regression model for the probability of receiving neoadjuvant therapy. The final propensity models for neoadjuvant bioselection included age, comorbidity score, current smoking, stage, disease subsite, and year of diagnosis for both comparisons. In Cox models of propensity-weighted datasets, DSS differed between the three treatment approaches.

In the propensity analysis, we found that DSS and OS were significantly improved in the neoadjuvant group compared to definitive chemoradiation/radiation [Hazard ratio 0.48, 95% CI: (0.29, 0.80), and Hazard ratio 0.48, 95% CI: (0.30, 0.78), respectively]. We also found that DSS for the definitive surgery group was significantly better compared to the neoadjuvant bioselection group, [Hazard ratio 0.14, 95% CI: (0.14, 0.82)] but we failed to find evidence for better overall survival in the surgery group [Hazard ratio 0.84, 95% CI: (0.46, 1.53)]. The results of all treatment comparisons remained statistically significant (or not significant) when we adjusted for age, stage, tumor site, comorbidities, and smoking for double robustness in our analysis models. In the doubly robust models, overall survival was again better for the neoadjuvant approach [HR .43, 95% C.I.: (.26, .69)] compared to chemoradiation and was similar to survival for the primary surgery group [HR .70, 95% C.I.: (.37, 1.338)] (Tables 3,4). The propensity-adjusted analyses confirmed the findings resulting from simple Cox univariable and multivariable models of treatment approach.

We next compared the potential benefit of primary surgery versus standard chemoradiation, among the 81 stage III/IV patients who were not selected for neoadjuvant chemoselection. We found no observed factors other than tumor stage and subsite that influenced the treatment choice. Among these patients, both glottic and stage IV patients were more likely to receive surgery. Adjustment for these factors in a stratified Cox proportional hazards model, showed that surgical treatment was associated with a decreased risk of disease-specific death both before and after adjusting for age, comorbidities, and current smoking, (HR=0.11 [95% C.I. 0.02, 0.56] and HR=0.14 [95% C.I.: 0.03, 0.68], $p=.0008$ and $p=.01$, respectively). Analysis of OS yielded similar, though slightly less dramatic results (HR=0.28 [95% CI: 0.09, 0.93] and HR=0.27 [95% CI: 0.08, 0.86], $p=0.04$ and $p=0.03$, respectively).

Functional Larynx Preservation

It is increasingly clear that preservation of laryngeal function is more important than simply preserving anatomic structure for assessing overall success. Thus, the status of larynx function as reflected by the presence of a feeding gastrostomy or tracheostomy at one year was recorded. Of the 94 patients with limited stage cancers, total laryngectomy as a salvage procedure for local recurrence was necessary in 6 patients; 5 following a failure of radiation, 1 after failure of chemoradiation and none were required after initial primary surgical resection. The overall organ preservation rate was 94%. Only one of the early patients required a tracheostomy and feeding tube at one year. For the 153 patients with advanced disease, primary total laryngectomy was performed in 26 patients and organ preserving surgery (supraglottic laryngectomy) was possible in 6 patients. Among these surgically treated patients, two had a feeding gastrostomy at one year. Of 50 patients treated with concurrent chemoradiation/radiation, a total of 4 laryngectomies (8%) were necessary for

persistent or locally recurrent disease. Only two patients required a tracheostomy, 4 had a feeding tube and one had both at one year. For these patients the functional larynx preservation rate was 78%. For the 71 patients assigned to neoadjuvant chemotherapy for bioselection, 11 laryngectomies were necessary after a poor response to induction chemotherapy (15%) and additionally 13 total laryngectomies were necessary after completing chemoradiation (18%). Thus, 66% the patients undergoing the neoadjuvant bioselective approach achieved organ preservation. For these patients, a total of 4 had only a feeding gastrostomy, 4 had only a tracheostomy and 5 had both at one year post treatment. The functional organ preservation (neither trach or G-tube) rate was 48%. The overall functional larynx preservation rate including primary surgery for the entire advanced disease cohort was 50%

Timing of Total Laryngectomy

We were interested in exploring whether the timing of salvage or primary total laryngectomy as part of an overall treatment plan influenced outcome. Even though numbers of patients undergoing total laryngectomy for advanced cancer were small, when the timing of total laryngectomy was analyzed, it was clear that OS and DSS favored the 11 planned laryngectomy patients who were selected for laryngectomy after neoadjuvant chemotherapy compared to the 26 primary total laryngectomy patients or the 13 patients who required a delayed salvage laryngectomy after chemoradiation. There were no failures (100% OS and DSS) among the patients undergoing planned laryngectomies performed as part of neoadjuvant bioselection. Overall and disease specific survival rates were similar for patients undergoing initial total laryngectomy (n=26) or late salvage laryngectomy after chemoradiation (n=13). Even though there was likely a negative selection bias for patients undergoing primary laryngectomy (i.e. more advanced disease such as T4a glottic or medical contraindications to chemotherapy), there were no significant differences in DSS comparing initial planned total laryngectomy (n=26) to the entire group of patients requiring secondary total laryngectomy after neoadjuvant or concurrent chemoradiation (n=24).

Discussion

Controversy exists regarding the optimal treatment approach for patients with advanced laryngeal cancer. Organ preserving surgery and combinations of chemotherapy with radiation as alternatives to total laryngectomy have been popularized to promote preservation of laryngeal function in patients with advanced disease. Results of randomized clinical trials of surgical versus non-surgical approaches however, have failed to show significant improvements in disease specific or overall survival or clear superiority of one approach over another^{14,24,30,31}. Despite this, concurrent chemoradiation approaches have been widely adopted based on the desire for larynx preservation and evidence from meta-analyses that concurrent chemoradiation is superior to radiation alone and may also be superior to neoadjuvant or sequential chemotherapy combined with radiation^{20–22}. Unfortunately, both surgical and non-surgical approaches have resulted in reported 5 year disease specific survival rates less than 50%. Although larynx preservation rates with concurrent chemoradiation are typically higher than those achieved with a sequential approach^{17,24}, no organ preservation approach has resulted in survival rates superior to total

laryngectomy. There are also concerns that long term toxicity, cost, and treatment related deaths may be greater compared to total laryngectomy^{10,11}. Additionally, survival results of patients enrolled in carefully controlled clinical trials of chemoradiation may not be generalizable to a non-select population of patients or reproduced outside of clinical trial settings^{12,32}.

The objective of the current study was to analyze long term survival outcomes for an unselected prospective patient cohort treated at a single institution that used an individualized treatment selection approach. Uniquely, our treatment selection algorithm incorporated the biologic tumor response to a single cycle of neoadjuvant chemotherapy to select definitive treatment for patients with advanced laryngeal cancer. This approach was based on our highly successful earlier Phase II clinical trial results^{26,27}. The findings from this non-randomized, observational cohort clearly demonstrate that the individualized treatment selection incorporating appropriate primary and salvage surgery in patients with advanced laryngeal cancer can achieve exceptional long term survival rates that are similar to those achieved in patients with more limited disease and are superior to results of other retrospective studies or randomized clinical trials. This was accompanied by a high overall rate of functional larynx preservation. The results also confirm 5 year DSS approximating 80% which is consistent with our previous Phase II clinical trials initiated in the early 1990's^{26,27}. The current results represent an important validation in a patient population that was not restricted by clinical trial eligibility criteria and included some patients receiving definitive chemoradiation at non-academic referral institutions but managed and followed by our head and neck oncology team. These results compare favorably to a recent large single institutional cohort study comparing surgery to non-surgical approaches in 235 patients with advanced supraglottic cancers that reported a 5-year survival rate of only 52% in both the surgical and non-surgical groups³³. Other large series and randomized clinical trials consistently report similar poor overall survival rates that range from 40–60%^{4,24,34–37}. The most recent SEER data comparing surgical to a non-surgical approach in 5394 patients from 1992–2009 reported 5 year DSS of 55% for surgery and 51% for non-surgical treatment with only 44% and 39% overall survival respectively⁴. A more recent analysis of 6797 patients from 2004–2012 also showed DSS in the range of 60%⁶. We believe the reason for the favorable results achieved in the current study are due to better treatment selection, although other reasons such as the experience of the treatment team and careful follow up could also be factors since early diagnosis and salvage of local tumor recurrences and treatment in an academic center have been associated with better survival, especially for complicated treatment^{34,37,38}.

The debate between primary total laryngectomy versus concurrent or neoadjuvant chemoradiation has not been resolved^{10,30,31}. Most studies document higher survival rates with primary surgery but at the sacrifice of laryngeal function. Further most chemoradiation studies indicate no survival benefit with addition of multicycle neoadjuvant chemotherapy^{19,20,22,39}. Our approach differs in that it incorporated a selection of patients for surgery using a single cycle of neoadjuvant chemotherapy, not for a therapeutic benefit, but for treatment selection. Univariate Cox regression analysis with respect to primary treatment showed that both primary surgery and neoadjuvant bioselection had significantly improved OS and DSS compared to definitive chemoradiation. Neoadjuvant and primary

surgery groups showed similar DSS. In multivariable analysis adjusting for confounding prognostic factors, similar results were found. Because survival outcomes of our overall patient cohort looked better with a primary surgical approach across all tumor stages, we were interested in analyzing the Hazard Ratios for all three treatment approaches in the advanced disease group. Relatively small sample sizes in these comparisons are reflected in the confidence intervals. To account for differences in patient and tumor characteristics and potential patient selection bias, we performed a propensity score adjusted Cox regression model analyses. In these analyses, OS and DSS were significantly improved in the neoadjuvant group over definitive chemoradiation/radiation. Likewise, primary surgery was superior to both chemoradiation and neoadjuvant bioselection for DSS, however OS outcomes were similar for primary surgery and neoadjuvant bioselection. Others have applied such propensity analyses to SEER data comparing surgery to chemoradiation and showed that survival outcomes did not differ when T4a patients were excluded³⁶. Because few institutions use neoadjuvant bioselection, we performed an additional stratified Cox regression analysis to further compare the results of primary surgery to primary chemoradiation after excluding the neoadjuvant group. Results of that analysis, showed that primary surgical treatment was associated with significantly reduced risk of death from cancer compared to concurrent chemoradiation. These findings are consistent with others in the literature^{6,36} and underscore the important role that primary surgery should play in treatment selection for patients with advanced, particularly T4a, cancer. Our results support the suggestion that careful selection criteria matching tumor and patient characteristics to treatment can enhance overall survival rates. The findings in this unselected series of patients with advanced cancers (Stages III, IV) suggest that using tumor response to a single cycle of neoadjuvant chemotherapy as bioselection for definitive therapy can contribute to an effective strategy for both non-responding and responding patients. There were no failures among patients selected for laryngectomy after neoadjuvant chemotherapy which contradicts the expected poor outcomes typically associated with non-responders after several cycles of neoadjuvant chemotherapy. Responders who were subsequently treated with concurrent chemoradiation also fared well, and though there were local recurrences requiring salvage laryngectomy, overall survival rates were excellent and 66% of patients were able to preserve their larynx. Functional larynx preservation rates were higher for the definitive chemoradiation group, but at a cost of decreased DSS.

The vast majority of chemoradiation trials for patients with advanced cancers document a 60–70% success rate for organ preservation but at a cost of toxicity, impairments in swallowing function and suspected late toxicity including chronic aspiration. These toxicities appear associated with larger initial tumor volumes and with radiation effects that are intensified by chemotherapy. Tumor volume has also been implicated as an important prognostic factor in chemoradiation treatment of advanced laryngeal cancer and less important in surgical management^{40,41}. This has led to a re-emphasis on use of primary total laryngectomy with appropriate voice rehabilitation as a good treatment alternative, particularly in patients with extensive T4a cancers, since swallowing function after treatment is often better and frequently quality of life outcomes are similar to larynx preservation^{15,42,43}. In fact, T4a cancers are often considered a contraindication for chemoradiation¹⁰. Most retrospective studies suggest better survival rates for T4a larynx

cancer patients treated with surgery compared to chemoradiation^{6,13,43–45}. Our prior work demonstrated survival rates for patients with T4a cancers that were similar to T3 patients when neoadjuvant bioselection was used with excellent preservation of speech and swallowing function^{27,46}. Our current study suffers, however, from not allowing direct, randomized comparison of the various treatment approaches or prospective quality of life assessments other than the accepted measure of presence of tracheostomy or feeding tube reflecting laryngeal function⁴⁷. Our prior work^{15,46} and that of others^{42,48} have suggested similar quality of life outcomes between primary laryngectomy and chemoradiation survivors. When patients are asked treatment preferences, the majority opt for chemoradiation, however, if survival differences favor surgery and if quality of life outcomes are poor with chemoradiation, an increasing number of patients will select surgery⁴⁹.

It was interesting to note that the rate of salvage laryngectomy (22%) was higher for patients receiving chemoradiation after neoadjuvant bioselection compared to primary chemoradiation (8%). This was likely due to the larger number of T4a patients undergoing neoadjuvant bioselection and closer follow up and more frequent salvage surgery compared to the primary chemoradiation group. Despite this, OS and DSS for the neoadjuvant bioselection group was superior to the definitive chemoradiation group and compared favorably to outcomes in patients treated with primary surgery. The worst DSS results were noted for patients treated with primary chemoradiation suggesting that lack of selection may have delayed appropriate surgery for some patients or perhaps other confounding negative factors associated with combined therapy such as longer overall treatment times or accelerated repopulation^{50–52}. It is unlikely that negative patient selection was responsible for the poorer results with definitive chemoradiation since the most medically compromised or very advanced disease patients were likely selected for primary surgery and the majority of T4a patients underwent bioselection. Laryngectomy patients, both primary and salvage laryngectomy did well overall, supporting the continued important role of surgery in the treatment of patients with advanced laryngeal cancer. Communicating these various nuances in outcomes, quality of life and long term morbidity to the patient is one of the most challenging issues in patient management and treatment selection. Clearly patient desires and expected speech and swallowing outcomes must be considered and may have greater importance than the actual treatment itself⁴⁹.

The major objective of neoadjuvant bioselection is to improve survival for all patients by matching an appropriate therapeutic approach to tumor biology. Not all patients benefit from chemotherapy and not all surgical patients achieve excellent survival. Clearly, trying to identify those who would benefit from each approach has obvious advantages that can translate into improved survival. The current results confirm our prior work^{26,27} and the findings of others that have adopted this approach⁵³ even for patients with T4a primary tumors. We relied on clinical estimates of tumor response after chemotherapy to decide between surgery or chemoradiation. It has been our experience that the most chemosensitive tumors respond dramatically and rapidly to neoadjuvant chemotherapy, making this clinical assessment after a single cycle relatively easy. Others have suggested that molecular biomarkers^{54,55} or combined pretreatment clinical characteristics and performance status⁵⁶ could be useful markers for selecting patients for larynx preservation and thereby avoiding inherent toxicities of chemotherapy. We have shown that clinical tumor response assessment

is probably better than relying on CT imaging⁵⁷, while other studies suggest that changes in PET imaging values may better reflect tumor response than either clinical or CT measures⁵³. What is clear is that the optimal method to assess chemotherapy or radiation sensitivity in order to select appropriate treatment has not yet been defined. Our prior studies of molecular biomarkers and neoadjuvant chemotherapy suggested that measures generally reflecting tumor aggressiveness and proliferation such as overexpression of p53, PCNA, Cyclin D1, or VEGF or aggressive histologic pattern of invasion correlate with favorable response to chemotherapy^{58–65}. Markers of immune response, such as elevated peripheral blood CD4 positive T lymphocyte levels or high levels of tumor infiltrating T cells have also shown promise as biomarkers^{55,66}. Combining several markers has been more promising than single marker correlations⁵⁵. Validation of previously suggested molecular biomarkers has not yet been performed in our patient cohort. Tissue microarrays have been constructed including some, but not all, of the cohort and should provide an important resource for exploring correlations of gene expression, tumor infiltrating lymphocyte levels and other biomarkers with chemotherapy response and survival outcomes.

There are obvious limitations to the interpretation of differences by treatment in this cohort study. This is primarily due to small sample sizes and a lack of randomization between treatment approaches. However, our patient inclusion was not limited by the strict patient eligibility criteria typically associated with clinical trials and patients were enrolled prospectively without bias by tumor site or stage. This is more representative of real-life treatment situations and outcomes than a clinical trial cohort. Treatment decisions were uniformly applied by a skilled multidisciplinary team and follow up was meticulous so that all patients were included in the analysis. These features are probable reasons why our results appear more favorable than those reported from SEER or NCDB data where analysis by treatment may be confounded by inclusion of patients treated for palliation and where outcomes and timing of salvage total laryngectomy may not be accurately recorded. In addition, analysis of tumor staging in SEER data is often inaccurate and rates of salvage laryngectomy are generally low³⁶. We believe our overall outcomes reflect the methods used to individualize treatment rather than just quality of care that might be attributed to an academic center with extensive experience^{38,67}. Primary surgery and planned surgical salvage were critical components in our treatment of advanced disease patients. Stage for stage, the best treatment strategy for maximizing patient survival and laryngeal function has not yet been identified. Although overall survival rate for our entire cohort of patients was excellent, it was concerning to see overall survival of patients with T2N0 (Stage II) cancers to be similar to those with Stage IV cancer (Figure 2). Similar unsatisfactory survival rates for patients with T2 cancers have been reported recently in a large nationwide study of unselected patients in Finland⁶⁸. To better understand these results, detailed analysis of our relatively small number of T2 larynx cancer patients (N= 34) is underway. But the results raise the question of whether under staging or under treatment of T2 patients may be responsible for declining survival rates for patients with intermediate disease as has been suggested in prior SEER data analysis^{69,70}. Importantly, primary surgical management for both early and advanced disease patients was confirmed as an important and highly effective treatment approach that must be considered in all personalized treatment recommendations.

This is critical when excellent voice restoration and swallowing function can be expected particularly if survival tradeoffs are not obvious.

Conclusions

Long term survival outcomes in this large, non-randomized prospective cohort suggest the potential benefit of careful patient selection and matching patient and tumor characteristics to an individualized treatment approach for patients with advanced laryngeal cancer. Exceptionally high survival rates were achieved in patients who participated in a bioselective treatment approach utilizing a single cycle of neoadjuvant chemotherapy. These rates were higher than any previously reported for patients with advanced laryngeal cancer and were similar to overall survival rates achieved in patients with limited disease. Excellent survival rates were also achieved in patients selected for primary surgery and for concurrent chemoradiation suggesting that the overall optimal treatment approach for patients with advanced laryngeal cancer has not yet been defined. The results also confirm prior studies indicating that the highest larynx preservation rates can be expected with a primary chemoradiation approach, however with somewhat lower overall survival compared to primary surgery or neoadjuvant bioselection. All three treatment approaches have a place in management algorithms. Further work is needed to define clinically relevant predictive biomarkers for treatment and to compare quality of life after treatment in order to help guide decision making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the many investigators in the University of Michigan Head and Neck Specialized Program of Research Excellence for their contributions to patient recruitment, assistance in data collection and encouragement including Carol R. Bradford, MD, Thomas E. Carey, PhD, Douglas B. Chepeha, MD, Sonia Duffy, PhD, Avraham Eisbruch, MD, Joseph Helman, DDS, Kelly M. Malloy, MD, Jonathan McHugh, MD, Scott A. McLean, MD, Tamara H. Miller, RN, Jeff Moyer, MD, Mark E. Prince, MD, Nancy Rogers, RN, Matthew E. Spector, MD, Nancy E. Wallace, RN, Heather Walline, PhD, Brent Ward, DDS, and Francis Worden, MD. We greatly thank our patients and their families who tirelessly participated in our survey and specimen collections. This work was supported by the University of Michigan Head and Neck Specialized Program of Research Excellence NIH/NCI P50CA097248, the UM Cancer Center P30CA046592 and the Sinabaldo and Diane Tozzi Research Fund.

References

1. Hoffman HT, Porter K, Karnell LH, Cooper JS, Weber RS, Langer CJ, Ang KK, Gay G, Stewart A, Robinson RA. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope*. 2006 Sep; 116(9 Pt 2 Suppl 111):1–13.
2. Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg*. 2007 Dec; 133(12):1270–6. [PubMed: 18086971]
3. Olsen KD. Reexamining the treatment of advanced laryngeal cancer. *Head Neck*. 2010 Jan; 32(1):1–7. DOI: 10.1002/hed.21294. [PubMed: 19953627]
4. Megwalu U, Sikora A. Survival outcomes in advanced laryngeal cancer. *JAMA Otolaryngol Head Neck Surg*. 2014; 140:855–860. [PubMed: 25144163]
5. Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute. <http://seer.cancer.gov/statfacts/html/laryn.html>

6. Harris BN, Bhuskute AA, Rao S, Farwell G, Bewley AF. Primary surgery for advanced-stage laryngeal cancer: a stage and subsite-specific survival analysis. *Head and Neck*. 2016 Mar 25. Epub ahead of print. doi: 10.1002/hed.24443
7. Hinni ML, Salassa JR, Grant DG, Pearson BW, Hayden RE, Martin A, Christiansen H, Haughey BH, Nussenbaum B, Steiner W. Transoral laser microsurgery for advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg*. 2007; 133(12):1198–204. [PubMed: 18086960]
8. Rödel RM, Steiner W, Müller RM, Kron M, Matthias C. Endoscopic laser surgery of early glottic cancer: involvement of the anterior commissure. *Head Neck*. 2009 May; 31(5):583–92. [PubMed: 19132720]
9. Hartl D, Ferlito A, Brasnu DF, Langendijk JA, Rinaldo A, Silver CE, Wolf GT. Evidence-Based Review of Treatment Options for Patients with Glottic Cancer. *Head Neck*. 2011; 33(11):1638–48. [PubMed: 21990228]
10. Strojan P, Haigentz M, Wolf GT, Bradford CR, Hartl DM, Langendijk JA, Rinaldo A, Eisbruch A, Mendenhall WM, Foratiere AA, Takes RP, Ferlito A. Chemoradiotherapy vs total laryngectomy for primary treatment of advanced laryngeal squamous cell carcinoma. *Oral Oncol*. 2013; 49(4): 283–6. DOI: 10.1016/j.oraloncology.2012.11.002 [PubMed: 23219843]
11. Haigentz M Jr, Vermorken JB, Foratiere AA, Corry J, Beitler JJ, Strojan P, Hartl DM, Rodrigo JP, Bradford CR, Rinaldo A, Takes RP, Mendenhall WM, Shaha AR, Wolf GT, Ferlito A. When is chemotherapy in head and neck squamous cell carcinoma not indicated ? *Eur Arch Otorhinolaryngol*. 2015; 272:781–787. [PubMed: 24525999]
12. Sanabria, A., Chaves, ALF., Kowalski, LP., Wolf, G., et al. Organ preservation with chemoradiation in advanced laryngeal cancer: the problem of generalizing results from randomized controlled trials. *Auris Nasus Larynx*. 2016. In press <http://dx.doi.org/10.1016/j.anl.2016.06.005>
13. Choi YS, Park SG, Song E, Cho S, Park M, Park KU, Lee K, Song I, Lee HJ, Jo D, Kim S, Yun H. Comparison of the therapeutic effects of total laryngectomy and a larynx-preservation approach in patients with T4a laryngeal cancer and thyroid cartilage invasion: a multicenter retrospective review. *Head and Neck*. 2016
14. The Department of Veteran 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]
15. Terrell JE, Fisher SG, Wolf GT. The VA Laryngeal Cancer Study Group: Long term quality of life after treatment for laryngeal cancer. *Arch Oto-HNS*. 1998; 124:964–974.
16. Lefebvre JL, Chevalier D, Lubinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst*. 1996 Jul 3; 88(13):890–9. [PubMed: 8656441]
17. Foratiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, Glisson B, Trotti A, Ridge JA, Chao C, Peters G, Lee DJ, Leaf A, Ensley J, Cooper J. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003 Nov 27; 349(22):2091–8. [PubMed: 14645636]
18. Lin SS, Massa ST, Varvares MA. Improved overall survival and mortality in head and neck cancer with adjuvant chemoradiotherapy in national databases. *Head Neck*. 2016; 38:208–215. [PubMed: 25225171]
19. Pignon JP, LeMaitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trial and 17,346 patients. *Radiotherapy and Oncology*. 2009; 92:4–14. [PubMed: 19446902]
20. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data MACH-NC Collaborative Group. *Lancet*. 2000; 355:949–55. [PubMed: 10768432]
21. Cohen EW, Karrison T, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck. *J Clin Oncol*. 2014; 32(25):2735–43. [PubMed: 25049329]
22. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, Clark J, Sarlis N, Lorch J, Beitler JJ, Limaye S, Riley S, Posner. Induction chemotherapy followed by concurrent

- chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol.* 2013; 14(3):257–64. [PubMed: 23414589]
23. Pfister DG, Spencer S, Brizel DM, Burtress B, Busse PM, Caudell JJ, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW, Gilbert J, Gillison ML, Haddad RI, Haughey BH, Hicks WL Jr, Hitchcock YJ, Jimeno A, Kies MS, Lydiatt WM, Maghami E, Martins R, McCaffrey T, Mell LK, Mittal BB, Pinto HA, Ridge JA, Rodriguez CP, Samant S, Schuller DE, Shah JP, Weber RS, Wolf GT, Worden F, Yom SS, McMillian NR, Hughes M. Head and neck cancers, Version 2.2014. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2014 Oct; 12(10):1454–87. [PubMed: 25313184]
 24. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, Morrison W, Glisson B, Trotti A, Ridge JA, Thorstad W, Wagner H, Ensley JF, Cooper JS. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol.* 2013 Mar 1; 31(7):845–52. [PubMed: 23182993]
 25. Haigentz M Jr, Cohen EE, Wolf GT, Strojan P, Eisbruch A, Ferlito A. The future of induction chemotherapy for head and neck squamous cell carcinoma. *Oral Oncol.* 2012; 48(11):1065–7. [PubMed: 22981388]
 26. Urba S, Wolf G, Eisbruch A, Worden F, Lee J, Bradford CR, et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. *J Clin Oncol.* 2006; 24:593–598. [PubMed: 16380415]
 27. Worden FP, Moyer J, Lee JS, Taylor JM, Urba SG, Eisbruch A, et al. Chemoselection as a strategy for organ preservation in patients with T4 laryngeal squamous cell carcinoma with cartilage invasion. *Laryngoscope.* 2009; 119:1510–1517. [PubMed: 19504552]
 28. Divi V, Worden FP, Prince MEP, Eisbruch A, Lee JS, Bradford CR, Chepeha DB, Teknos TN, Hogikyan ND, Moyer J, Tsien CI, Urba SG, Wolf GT. Chemotherapy alone for organ preservation in advanced laryngeal cancer. *Head Neck.* 2010; 32(8):1040–7. [PubMed: 19953609]
 29. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med.* 2014 Mar 30; 33(7):1242–58. Epub 2013 Sep 30. DOI: 10.1002/sim.5984 [PubMed: 24122911]
 30. Lagha A, Chraïet N, Labidi S, Rifi H, et al. Larynx preservation: What is the best non-surgical strategy? *Crit Rev Oncol Hemat.* 2013; 88:447–458.
 31. Horn S, Ozsahin M, Lefebvre JL, Horiot JC, Lartigau E. on behalf of AROME. Larynx preservation: what is the standard therapy. *Crit Rev Oncol Hematol.* 2012; 84:e97–e105. [PubMed: 21185198]
 32. Chavez-MacGregor M, Giordano SH. Randomized clinical trials and observational studies: is there a battle? *J Clin Oncol.* 2016; 34:772–73. [PubMed: 26786920]
 33. Elegbede AI, Rybicki LA, Adelstein DJ, et al. Oncologic and functional outcomes of surgical and nonsurgical treatment of advanced squamous cell carcinoma of the supraglottic larynx. *JAMA Otolaryngol Head Neck Surg.* 2015; 141:1111–1117.
 34. Chen AY, Fedewa S, Zhu J. Temporal trends in the treatment of early- and advanced-stage laryngeal cancer in the United States, 1985–2007. *Arch Otolaryngol Head Neck Surg.* 2011; 137(10):1017–24. [PubMed: 22006780]
 35. Timmermans AJ, van Dijk BA, Overbeek LI, van Velthuisen MF, 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 Apr; 38(Suppl 1):E1247–55. Epub 2015 Aug 28. DOI: 10.1002/hed.24200 [PubMed: 26315454]
 36. O'Neill CB, O'Neill JP, Atoria CL, Baxi SS, Henman MC, Ganly I, Elkin EB. Treatment complications and survival in advanced laryngeal cancer: a population based analysis. *Laryngoscope.* 2014; 124:2707–13. [PubMed: 24577936]
 37. Forastiere AA, Weber RS, Trotti A. Organ preservation for advanced larynx cancer: issues and outcomes. *J Clin Oncol.* 2015; 33:3262–8.

38. Boero IJ, Paravati AJ, Xu B, Cohen EEW, et al. Importance of radiation oncologist experience among patients with head-and-neck cancer treated with intensity-modulated radiation therapy. *J Clin Oncol*. 2016
39. Chen JH, Yen Y, Liu S, Yuan S, Wu L, et al. Outcomes of induction chemotherapy for head and neck cancer patients. A combined study of two national cohorts in Taiwan. *Medicine*. 2016; 95:1–7.
40. Issa MR, Samuels E, Bellile E, Shalabi FL, Eisbruch A, Wolf G. Tumor volumes and prognosis in laryngeal cancer. *Cancers*. 2015; 7:2236–2261. [PubMed: 26569309]
41. Timmermans AJ, Lange CAH, de Bois JA, van Werkhoven E, Hammin-Vrieze O, et al. Tumor volume as a prognostic factor for local control and overall survival in advanced larynx cancer. *Laryngoscope*. 2016; 126:E60–67. [PubMed: 26333005]
42. Trivedi NP, Swaminathan DK, Thankappan K, Chatni S, Kuriakose MA, Iyer S. Comparison of quality of life in advanced laryngeal cancer patients after concurrent chemoradiotherapy vs. total laryngectomy. *Otolaryngol Head Neck Surg*. 2008; 139:702–707. [PubMed: 18984267]
43. Rosenthal DI, Mohamed AS, Weber RS, et al. Long-term outcomes after surgical or nonsurgical initial therapy for patients with T4 squamous cell carcinoma of the larynx: A 3-decade survey. *Cancer*. 2015; 121(10):1608–19. [PubMed: 25586197]
44. Gourin CG, Conger BT, Sheils WC, Bilodeau PA, Coleman TA, Porubsky ES. The effect of treatment on survival in patients with advanced laryngeal carcinoma. *Laryngoscope*. 2009; 119(7):1312–7. [PubMed: 19444887]
45. Dziegielewski PT, O'Connell DA, Klein 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]
46. Fung K, Lyden TH, Lee J, Urba SG, Worden F, Eisbruch A, Tsien C, Bradford CR, Chepeha DB, Hogikyan ND, Prince MEP, Teknos T, Wolf GT. Voice and swallowing outcomes of an organ preservation trial for advanced laryngeal cancer. *Intl J Rad Oncol Biol Phys*. 2005; 63(5):1395–9.
47. Lefebvre J-L, Ang KK. Larynx Preservation Consensus Panel. Larynx preservation clinical trial design key issues and recommendations-a consensus panel summary. *Head Neck*. 2009; 31:429–41. [PubMed: 19283793]
48. LoTempio MM, Wang KH, Sadeghi A, et al. Comparison of quality of life outcomes in laryngeal cancer patients following chemoradiation vs. total laryngectomy. *Otolaryngol Head Neck Surg*. 2005; 132:948–53. [PubMed: 15944570]
49. Hamilton DW, Bins JE, McMeekin P, Pedersen A, Steen N, De Soyza A, Thomson R, Paleri V, Wilson JA. Quality compared to quantity of life in laryngeal cancer: a time trade-off study. *Head Neck*. 2016; 38:E631–E637. [PubMed: 25832305]
50. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *International journal of radiation oncology, biology, physics*. 2006; 64(1):77–82.
51. Yom SS. Accelerated repopulation as a cause of radiation treatment failure in non-small cell lung cancer: review of current data and future clinical strategies. *Semin Radiat Oncol*. 2015; 25:93–9. [PubMed: 25771413]
52. Meade S, Sanghera P, McConkey C, Fowler J, et al. Revising the radiobiological model of synchronous chemotherapy in head-and-neck cancer: a new analysis examining reduced weighting of accelerated repopulation. *Int J Radiat Oncol Biol Phys*. 2013; 86:157–63. [PubMed: 23332227]
53. Semrau S, Schmidt D, Lell M, Waldfahrer F, Lettmaier S, Kuwert T, Iro H, Fietkau R. Results of chemoselection with short induction chemotherapy followed by chemoradiation or surgery in the treatment of functionally inoperable carcinomas of the pharynx and larynx. *Oral Oncol*. 2013; 49:454–60. [PubMed: 23321550]
54. Bradford CR, Kumar B, Bellile E, Lee J, Taylor J, DeSilva N, Cordell K, Kleer C, Kupfer R, Kumar P, Urba S, Worden F, Eisbruch A, Wolf GT, Teknos TN, Prince ME, Chepeha DB, Hogikyan ND, Moyer JS, Carey TE. Biomarkers in Advanced Larynx Cancer: Triological Society Thesis. *Laryngoscope*. 2014; 124:179–87. [PubMed: 23775802]

55. Dewyer NA, Wolf GT, Light E, Worden F, Urba S, Eisbruch A, Bradford CR, Chepeha DB, Prince ME, Moyer J, Taylor J. Circulating CD4- Positive Lymphocyte Levels Predict Response to Induction Chemotherapy in Patients with Advanced Laryngeal Cancer. *Head Neck*. 2014; 36:9–14. [PubMed: 23765859]
56. Sherman EJ, Fisher SG, Kraus DN, et al. TALK score: development and validation of a prognostic model for predicting larynx preservation outcome. *Laryngoscope*. 2012; 122:1043–50. [PubMed: 22374653]
57. Chepeha DB, Sacco AG, Oxford LE, Karamchandani R, Miller TH, Teknos TN, Bradford CR, Eisbruch A, Worden FM, Urba SG, Mukherji SK, Bui C, Frey KA, Wolf GT, Lee JS. Advanced squamous cell carcinoma of the oropharynx: efficacy of positron emission tomography and computed tomography for determining primary tumor response during induction chemotherapy. *Head Neck*. 2009; 31(4):452–60. [PubMed: 19189338]
58. Kumar B, Cordell KG, D'Silva N, Prince ME, Adams ME, Fisher SG, Wolf GT, Carey TE, Bradford CR. Expression of p53 and Bcl-xL as predictive markers for larynx preservation in advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg*. 2008; 134(4):363–9. [PubMed: 18427001]
59. Teknos TN, Cox C, Barrios M, Chepeha DB, Bradford CR, Fisher SG, Wolf GT. Tumor angiogenesis as a predictive marker for organ preservation in patients with advanced laryngeal cancer. *Laryngoscope*. 2002; 112:844–851. [PubMed: 12150616]
60. Teknos TN, Cox C, Yao S, Chepeha DB, Wolf GT, Bradford CR, Carey TE, Fisher SG. Elevated serum vascular endothelial growth factor and decreased survival in advanced laryngeal cancer. *Head and Neck*. 2002; 24:1004–1011. [PubMed: 12410536]
61. Trask DK, Wolf GT, Bradford CR, Fisher SG, Devaney K, Johnson M, Singleton T, Wicha M. Expression of Bcl-2 family proteins in advanced laryngeal squamous cell carcinoma: correlation with response to chemotherapy and organ preservation. *Laryngoscope*. 2002; 112:638–44. [PubMed: 12150516]
62. Bradford CR, Wolf GT, Carey TE, Zhu S, Beals T, Truelson J, McClatchey KD, Fisher SG. Predictive markers for response to chemotherapy, organ preservation and survival in patients with advanced laryngeal carcinoma. *Otolaryngol Head Neck Surg*. 1999; 121(5):534–538. [PubMed: 10547465]
63. Bradford CR, Zhu S, Poore J, Beals TF, Fisher SG, Carey TE, Wolf GT, and Department of Veterans Affairs Laryngeal Cancer Study Group. p53 mutation as a prognostic marker in advanced laryngeal carcinoma. *Arch Otolaryngol*. 1997; 123:605–609.
64. Gregg CM, Beals TF, McClatchey KD, Fisher SG, Wolf GT. DNA content and tumor response to induction chemotherapy in patients with advanced laryngeal squamous cell carcinoma. *Otolaryngol Head Neck Surg*. 1993; 108:731–737. [PubMed: 8516011]
65. Truelson JM, Fisher S, Beals TF, McClatchey KD, Wolf GT. DNA content and histologic growth pattern correlate with prognosis in patients with advanced squamous cell carcinoma of the larynx. *Cancer*. 1992; 70:56–62. [PubMed: 1606547]
66. Nguyen N, Bellile E, Thomas D, McHugh J, Rozek L, Virani S, Peterson L, Carey T, Walline H, Moyer J, Spector M, Perim D, Prince M, McLean S, Bradford CR, Taylor JMG, Wolf GT. The Head and Neck SPORE Program. Tumor infiltrating lymphocytes and survival in patients with head and neck squamous carcinoma. *Head and Neck*. Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).
67. Wuthrick EJ, Zhang Q, Machtay M, Rosental DI, et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. *J Clin Oncol*. 2015; 33(2):156–64. [PubMed: 25488965]
68. Haapaniemi A, Koivunen P, Saarilahti K, Kinnunen I, et al. Laryngeal cancer in Finland: A 5-year follow-up study of 366 patients. *Head & Neck*. 2016; 38:36–43. [PubMed: 24996171]
69. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer*. 2005 May 1; 114(5):806–16. [PubMed: 15609302]
70. Wolf GT. Re-Examining the Treatment of Advanced Laryngeal Cancer – The VA Laryngeal Cancer Study Re-Visited (Invited Commentary). *Head Neck*. 2010; 32(1):7–14. [PubMed: 19953621]

Figure 1.
Distribution of 247 patients according to clinical tumor stage, primary treatment modality and frequency of total laryngectomy.

Figure 2.

Overall (OS) and disease-specific Kaplan Meier survival (DSS) curves for 247 patients with laryngeal squamous carcinoma grouped by clinical tumor stage. Differences in outcomes were apparent comparing Stage I to Stage IV patients for DSS and OS. Overall survival rates did not differ significantly for other stage comparisons.

Figure 3. Overall and disease-specific survival for 247 patients with laryngeal squamous carcinoma according to initial primary treatment modality. Survival outcomes were significantly better for patients treated with primary surgery.

Figure 4.

Overall and disease-specific survival for patients with Stage I and II laryngeal cancer according to primary treatment modality. Overall survival rates for early disease patients were significantly better for primary surgery compared to radiation or chemoradiation, however, differences in DSS did not reach statistical significance. The treatment differences were confounded by differences in patient characteristics such as T class. Surgically treated patients were significantly more likely to be lower stage ($p<0.001$). After excluding the 9 patients with in situ carcinoma and controlling for stage in a multivariable Cox model, neither OS and DSS differences remained statistically significant (data not shown.)

Figure 5.

Overall and disease-specific survival (DSS) for 153 patients with advanced (Stage III, IV) laryngeal cancer according to planned initial treatment modality. Although overall survival curve comparisons did not differ significantly by planned treatment, planned chemoradiation tended to have worse overall and disease specific outcomes. By Cox regression analysis, DSS was significantly improved in the neoadjuvant group over definitive chemoradiation/radiation without induction selection [Hazard ratio 0.27, 95%CI: (0.11, 0.68)] after controlling for age, stage (III vs IV), gender, and current smoking and DSS for the neoadjuvant group was similar to the surgery group, [Hazard ratio 2.80, 95%CI: (0.62, 12.61)].

Table 1

Patient, Tumor, and Treatment Characteristics

Characteristic	Category	N (%)
Gender	Male	191 (77%)
	Female	56 (23%)
Smoking Status	Never	18 (7%)
	Past	60 (25%)
	Current	165 (68%)
ACE-27* Comorbidity Overall Score	None	49 (20%)
	Mild	112 (45%)
	Moderate	61 (25%)
	Severe	25 (10%)
Subsite	Glottic	115 (47%)
	Supraglottic	132 (53%)
Stage	I	60 (24%)
	II	34 (14%)
	III	53 (21%)
	IV	100 (40%)
Neoadjuvant Chemo.	Yes	71 (29%)
	No	176 (71%)
Treatment	Chemoradiation	115 (47%)
	Radiation	56 (23%)
	Surgery	76 (31%)

Characteristic category percentages may not add to 100 due to rounding.

* The ACE-27 grades specific diseases and conditions into 1 of 3 levels of comorbidity, grade 1 (mild), grade 2 (moderate), or grade 3 (severe), according to the severity of individual organ decompensation and prognostic impact. Once the patient's individual diseases or comorbid conditions were classified, an overall comorbidity score (none, mild, moderate, or severe) was assigned based on the highest ranked single ailment. In the cases in which 2 or more moderate ailments occurred in different organ systems or disease groupings, the overall comorbidity score was designated as severe.

Table 2

Planned Approach by T class in advanced (Stage III, IV) laryngeal cancer group only (n=153):

T Classification	Neoadjuvant Selection	Radiation/Chemoradiation	Surgery	Total
T1	1 (25%)	2 (50%)	1 (25%)	4
T2	6 (32%)	10 (53%)	3 (16%)	19
T3	32 (45%)	27 (38%)	12 (17%)	71
T4	32 (54%)	11 (19%)	16 (27%)	59
Total	71	50	32	153

Row percentages may not add to 100 due to rounding.

Table 3

Propensity adjusted multivariable Cox proportional hazards model results for overall survival in patients with advanced laryngeal (Stage III, IV) cancer comparing neoadjuvant bioselection approach to definitive chemoradiation.

Parameter		Hazard Ratio	95% Hazard Ratio Confidence Limits	
Treatment Approach	Neoadjuvant Selection	0.43 *	0.27	0.70
	Definitive Chemorad/Rad	ref.		
Age at Diagnosis (years)		1.05 *	1.02	1.08
Stage	IV	2.42 *	1.35	4.35
	III	ref.		
Disease Subsite	Glottic	0.60	0.30	1.21
	Supraglottic	ref.		
Smoking status	Current smoker	1.40	0.77	2.56
	All others	ref.		
ACE-27 Comorbidities	none	0.29 *	0.12	0.71
	mild	0.47 *	0.22	1.00
	moderate	0.44 *	0.19	1.02
	severe	ref.		

*
p-value < 0.05

Table 4

Propensity adjusted multivariable Cox proportional hazards model results for overall survival in patients with advanced (Stage III, IV) laryngeal cancer comparing neoadjuvant bioselection to primary surgery approach.

Parameter		Hazard Ratio	95% Hazard Ratio Confidence Limits	
Treatment Approach	Primary Surgery	0.70	0.37	1.34
	Neoadjuvant Selection	ref.		
Age at Diagnosis (years)		1.05 [*]	1.00	1.09
Stage	IV	1.94	0.73	5.15
	III	ref.		
Disease Subsite	Glottic	1.12	0.58	2.19
	Supraglottic	ref.		
Smoking status	Current smoker	2.42 [*]	0.95	6.15
	All others	ref.		
ACE-27 Comorbidities	none	0.08 [*]	0.01	0.60
	mild	0.44	0.15	1.26
	moderate	0.84	0.28	2.49
	severe	ref.		

*
p-value < 0.05