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Original Research Article

Imaging response assessment for predicting outcomes after bioselection chemotherapy in larynx cancer: A secondary analysis of two prospective trials

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ABSTRACT

Background and purpose: Bioselection with induction chemotherapy in larynx cancer is associated with excellent larynx preservation and disease-specific survival but requires visual inspection of the primary tumor. We retrospectively compare clinical and imaging response in bioselected patients to develop predictive models of surgeon-assessed response (SR), laryngectomy-free survival (LFS), and overall survival (OS) in bioselected patients.

Materials and methods: In a secondary analysis of patients on two single-institution bioselection trials, model building used a regularized regression model (elastic-net) and applied nested cross-validation. Logistic regression-based model was used to predict SR and Cox proportional hazard-based models were used to predict LFS and OS.

Results: In 115 patients with a median age of 57 years, most patients had supraglottic tumors (73.0%) and T3/T4 disease (94.8%). Definitive treatment was chemoradiation in 76.5% and laryngectomy in 23.5%. Change in primary tumor (OR = 5.78, $p < 0.001$) and N-classification (OR = 1.64, $p = 0.003$) predicted SR (AUC 0.847). Change in tumor volume (HR = 0.58, $p < 0.001$) predicted LFS (c-index 0.724). N-classification (HR = 1.48, $p = 0.04$) and pre-chemotherapy tumor volume (HR = 1.30, $p = 0.174$) predicted OS (c-index 0.552).

Conclusions: Imaging offers a non-invasive opportunity to evaluate response to induction chemotherapy, complementary to surgeon assessment. Further evaluation of approaches to bioselection that optimize generalizability of this paradigm are needed, and clinical trials utilizing imaging to predict outcomes including LFS are warranted.

1. Introduction

The treatment of locally advanced laryngeal cancer has seen an arc in the past thirty years. The historic standard of care was laryngectomy with adjuvant radiation. With the publication of the Veterans Affairs Laryngeal Cancer Study in 1991 [1] followed by RTOG 9111 [2] and EORTC 24891 [3], organ preservation approaches emerged as an option for these locally advanced patients. Widespread adoption of this approach, even in very locally advanced patients, initially led to concerns for decreased survival of patients treated with chemoradiation approaches [4,5]. A need for improved patient selection to identify patients who might benefit from organ preservation without concern for

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decreased survival was needed.

Typical courses of induction chemotherapy utilized in locally advanced cancers include three cycles of high-dose triplet chemotherapy regimens [6,7]. In the 1990s, after the successful completion of the Veterans Affairs Laryngeal Cancer Study trial [1], another study attempting to further improve rates of locoregional recurrence in patients treated with chemoradiation by adding radiation acceleration [8] stemmed from the hypothesis that decreasing treatment time would allow for decrease in accelerated clonogen regrowth [9]. In this study, a correlation was seen between response after a single cycle of chemotherapy and outcomes, leading to another phase II study [10] that utilized a single cycle of chemotherapy as a bioselection tool to select a course of treatment (laryngectomy versus chemoradiation), again driven by the desire to minimize total treatment time due to concern for accelerated repopulation. This study showed that cancers with rapid response to induction chemotherapy have a favorable response to definitive chemoradiotherapy and may even have improved survival [10].

These insights forms the basis for a bioselection approach to laryngeal cancer, where limited induction chemotherapy is given to assess disease response and optimal therapy is selected on the basis of response, ideally matching tumor biology with appropriate therapy to optimize survival and minimize toxicity. This approach has been shown to offer excellent survival and cancer specific survival rates, comparable to upfront surgery and potentially better than unselected concurrent chemoradiation in trial patients as well as unselected retrospective cohorts [11]. At the University of Michigan, this approach is favored for locally advanced laryngeal cancer due to its ability to select for patients with high likelihood of benefiting from organ preservation, even in the case of cT4a cancers, while typically limiting chemotherapy to one cycle and thus limiting chemotherapy toxicity. Furthermore, non-responding patients may be offered primary laryngectomy without incurring the swallowing and aspiration morbidity associated with definitive chemoradiation or the higher surgical complication rates seen in salvage laryngectomy [12].

Barriers to widespread adoption of a bioselection approach include challenges in assessing treatment response to chemotherapy. The gold standard for assessment of response is surgeon assessment based on pre- and post-chemotherapy visualization most commonly through operative direct laryngoscopy, as has been done on practice-changing trials such as the VA Larynx [1] and EORTC 24891 [3] trials. This can be subjective and may not allow for accurate assessment of submucosal response. Other studies, such as RTOG 9111, did include imaging [13]. It remains unclear how to best incorporate both imaging and direct visualization, and how these may predict outcomes. The current study was performed to devising a more robust bioselection algorithms to assess the role of imaging and labs to predict treatment response to induction chemotherapy, as well as analyzing laryngectomy-free survival (LFS), and overall survival (OS).

2. Materials and methods

2.1. Patients and data

This study is a retrospective analysis of patients treated with a bioselection approach for locally advanced laryngeal cancer that was approved by the University of Michigan's Institutional Review Board (HUM00105976). Patients in our model training set were treated on two prospective institutional trials (UMCC 9520 [10] and NCT 01633541 [14]) and patients in the model validation set were treated off-trial with a similar bioselection approach. Briefly, all patients received pre-treatment imaging and surgeon assessment prior to the initiation of therapy. Patients received platinum-based induction (typically a single cycle of cisplatin and fluorouracil), followed by post-treatment imaging and surgeon assessment three weeks later as mandated by trials. Pre-treatment imaging was obtained within 4 weeks of enrollment. Patients who had a $\geq$50% response to therapy by surgeon assessment received chemoradiation; those with <50% response received total laryngectomy. Concurrent chemoradiation was delivered with cisplatin or with carboplatin/paclitaxel for cisplatin-ineligible patients. Patients receiving at least one cycle of induction chemotherapy with pre- and post-chemotherapy contrast-enhanced computed tomography scans available for review were included in this analysis.

Clinical variables were acquired from patient electronic medical records and included tumor subsite, T-classification, and N-classification (latter both based on American Joint Committee on Cancer 7th edition staging). Laboratory-based features included neutrophil–lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR) calculated from pre-treatment complete blood counts, and both of these were treated as as binary variables determined by cut-points reported previously in the literature.[15] Specifically, NLR was dichotomized at 0 for NLR values $\leq$2.8 and 1 otherwise, while LMR was dichotomized at 0 for LMR values $\geq$2.8 and 1 otherwise.

To acquire image-based features, primary tumor structures were contoured on pre-chemotherapy and post-chemotherapy (after cycle one) CT images by two physicians (LAG, EMJ) with all contours reviewed by a fourth attending radiation oncologist (MM) using clinical software (Varian Medical Systems, Inc. Eclipse Treatment Planning System). CT-based variables investigated were pre-chemotherapy primary tumor volume, and the percent reduction in tumor volume after chemotherapy.

2.2. Model training and validation

To develop predictive models of surgeon-assessed response (SR) and analyze patient responses, we utilized a regularized regression method known as Elastic-net that linearly combines the L1 and L2 penalties of the Lasso and ridge methods [16]. This kind of modeling is demonstrated to provide robust prediction when the sample size is limited as in our case. In order to mitigate overfitting pitfalls and statistical bias we applied a nested-cross validation (NCV) technique [17].

Trial patients were used to build and train the model; the subset of patients that were treated off-trial were purposefully selected as a validation dataset to increase patient heterogeneity and measure model generalization (see Fig. 1 for schema) [18]. Feature selection was performed using elastic-net and validated using NCV for regularization parameter optimization and unbiased relevant feature identification in MATLAB. A logistic regression-based model was used to predict the surgeon-assessed chemotherapy response, defined as $\geq$50% shrinkage of tumor volume with selected feature significance assessed by odds ratio (OR) and model prediction with the area under the receiver operating characteristic curve (AUC). Cox proportional hazards models were used to predict LFS and OS with selected feature significance assessed by hazard ratio (HR) and model prediction with Harrell's concordance index (c-index). A p-value < 0.05 is considered statistically significant.

3. Results

3.1. Patients and treatment

We identified 289 patients undergoing bioselection from 2003 to

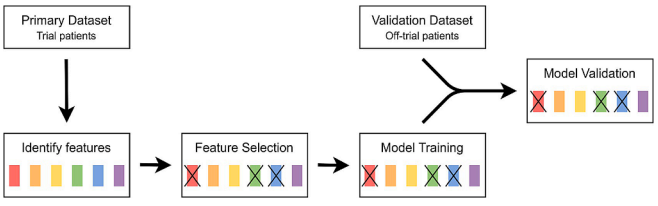

Fig. 1. Schema of model building utilizing the primary dataset to identify and select features, then training and validating the model.

2019. Of these, 115 had imaging information available for analysis including pre-induction and post-induction chemotherapy contrast-enhanced computed tomography. There were 93 patients treated on bioselection clinical trials that were used for the model training dataset, and 22 patients treated with bioselection off-trial were reserved for model validation. Patients had a median age of 57 years, with the majority of patients having primary tumor site in the supraglottic larynx (73.0%) and with T3/T4 tumors (94.8%). The median primary tumor size was 21.8 cc (see Table 1). By surgeon assessment, 67.8% (n = 78) of patients had ≥50% tumor response; on imaging, the average primary tumor volume reduction was 39.4% (standard deviation 34.3%). Pre-induction imaging was obtained at a median of 13 days prior to chemotherapy (standard deviation, 16 days); post-induction imaging was obtained approximately 21 days after chemotherapy. There was a mean of 1.7 days between post-chemotherapy CT imaging and surgeon assessment of response (standard deviation, 2.1 days).

After one cycle of induction chemotherapy, approximately two-thirds of patients had ≥50% tumor response (n = 78, 67.8%) to induction chemotherapy based on surgeon assessment during direct laryngoscopy, and 44.3% (n = 51) had ≥50% tumor response based on CT imaging. Fig. 2 shows representative images of a favorable response to induction chemotherapy.

Fig. 3 demonstrates the breakdown of treatment for patients. Twenty-seven patients (23.5%) underwent total laryngectomy as definitive treatment after insufficient response to induction chemotherapy based on surgeon assessment, with all but two of these patients receiving either adjuvant radiation or adjuvant chemoradiation after laryngectomy. Eighty-eight patients (76.5%) received organ preservation with treatment with definitive chemoradiation. Ten patients who did not initially have good response to the first cycle of induction chemotherapy underwent definitive chemoradiation; seven underwent a planned second cycle of induction chemotherapy after insufficient response to the first cycle and had a ≥50% response with the second cycle of induction chemotherapy, subsequently receiving definitive chemoradiation. These patients were treated in a different manner according to patient and physician preference. Three patients were recommended to undergo laryngectomy but refused and underwent definitive chemoradiation (two of whom later had salvage laryngectomies).

At time of analysis, 33.9% (n = 39) of patients had died and 39.1% (n = 45) had a laryngectomy.

Of patients who underwent definitive chemoradiation, 18.1% (n = 16) ultimately underwent salvage laryngectomy for local recurrence. Two additional patients underwent laryngectomy for non-oncologic reasons (one for non-functional larynx, and another for fistula formation). Two additional patients were recommended to undergo salvage laryngectomy but did not receive due to patient preference.

Table 1
Demographics of the training and v dataset.

	Training Dataset (n = 93) N (%)	Validation Dataset (n = 22) N (%)
Clinical Information		
Age (years, median, range)	57 (19–82)	58.5 (29–77)
Pre-treatment tumor size (cc, mean, range)	23.85 (1.1–74.6)	13.26 (2–37.9)
Site		
Supraglottis	70 (75.3%)	14 (63.6%)
Glottis	20 (21.5%)	5 (22.7%)
Hypopharynx	3 (3.2%)	3 (13.6%)
T-classification		
T1	0 (0%)	1 (4.5%)
T2	3 (3.2%)	2 (9.1%)
T3	39 (41.9%)	10 (45.5%)
T4	41 (54.8%)	9 (40.9%)
N-classification		
N0	33 (35.5%)	8 (36.4%)
N1	11 (11.8%)	1 (4.5%)
N2a	2 (2.2%)	0 (0%)
N2b	22 (23.7%)	4 (18.2%)
N2c	25 (26.9%)	6 (27.3%)
N3	0 (0%)	3 (13.6%)
Median Neutrophil-Lymphocyte Ratio (median, range)	2.88 (0.88–56)	2.84 (0.44–10.85)
Median Lymphocyte-Monocyte Ratio (median, range)	1.55 (0.28–5.67)	2.58 (0.70–12.14)
Treatment Information		
Number of days between computed tomography imaging and surgeon assessment of response (mean, standard deviation)	1.8 (2.2)	1.1 (0.97)
Tumor Response (by surgeon assessment)		
<50%	33 (35.5%)	4 (18.2%)
≥50%	60 (64.5%)	18 (81.8%)
Average Tumor Reduction by imaging, % (standard deviation)	35.45% (34.78%)	55.98% (26.95%)
Treatment received		
Total laryngectomy	23 (24.7%)	4 (18.2%)
Chemoradiation	70 (75.3%)	18 (81.8%)

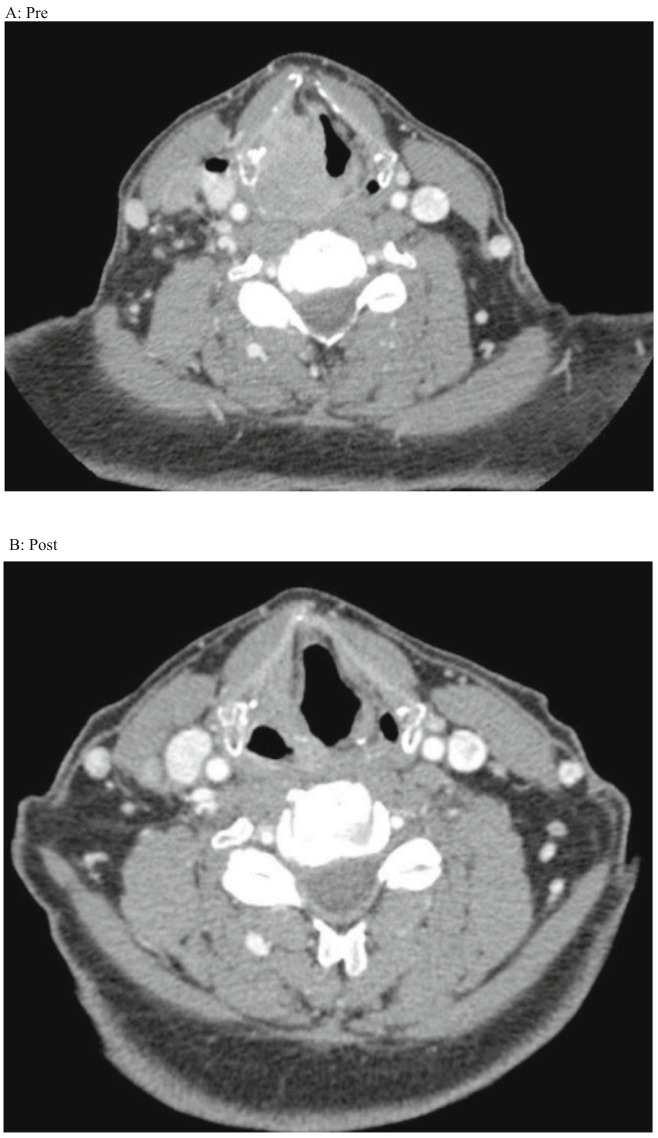

Fig. 2. 61 year old male with a cT3N2b supraglottic squamous cell carcinoma who responded well to induction chemotherapy. Panel A represents a pre-chemotherapy computed tomography scan, and panel B represents response after one cycle of induction chemotherapy.

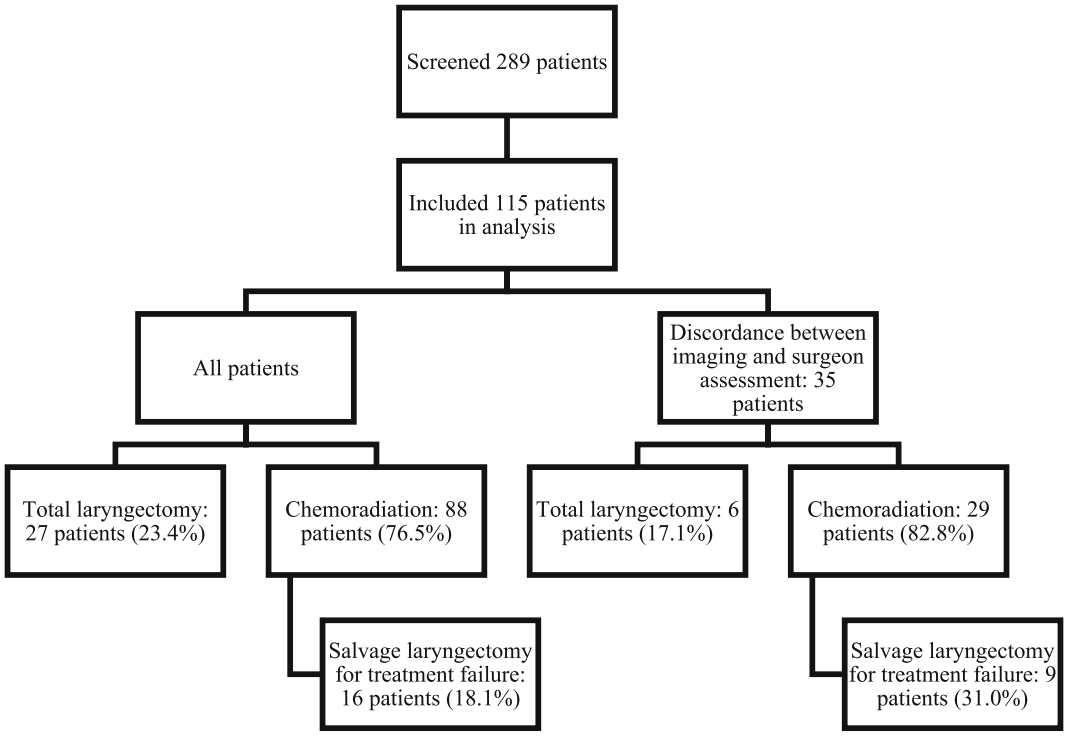

Fig. 3. Diagram demonstrating treatment for patients included on current study, for all patients and for the discordant patients.

3.2. Discordance between surgeon assessment and CT imaging

There were 35 patients (30.4%) with discordance between surgeon assessment and CT imaging. Of these, 31 patients had a response that was deemed to be ≥50% by surgeon assessment but <50% by CT imaging. Of note, the discordant patients had high rates of locally advanced primary tumors with paraglottic space involvement. Two of these patients had exactly 50% response based on surgeon assessment and the decision was made to proceed with total laryngectomy. The remaining 29 patients were treated with definitive chemoradiation. Of these patients treated with organ preservation, 8 died prior to local recurrence and 9 patients required salvage laryngectomy, representing a 31.0% rate of salvage laryngectomy for the discordant patients.

Four patients had <50% response on initial surgeon assessment but ≥50% by CT imaging. Of these patients, one patient went to total laryngectomy for treatment and three received a planned additional cycle of induction chemotherapy. These latter three ultimately achieved ≥50% response, and thus received definitive chemoradiation (one later receiving a salvage laryngectomy due to local recurrence).

3.3. Model features

Features for selection in model building included T-classification, N-classification, tumor subsite, NLR, LMR, age, tumor volume, and percent tumor reduced after chemotherapy. CT volume according to tumor contour was evaluated as well as two-dimensional tumor greatest dimension measurements, and the latter was not selected in the model building process. Subsequently analyzed models focused on clinical and laboratory features, as well as information on contoured tumor volumes. Summary of model features and testing are in Tables 2 and 3.

3.4. Surgeon assessment of induction response

Two-thirds of patients had ≥50% tumor response (n = 78, 67.8%) to induction chemotherapy based on surgeon assessment during direct laryngoscopy. A model was built to predict for surgeon assessment of induction chemotherapy response as ≥50%. Feature selection for model building selected two features as statistically significant for surgeon assessment of induction chemotherapy response: change in primary tumor volume as assessed on CT imaging (OR = 5.78, $p < 0.001$), and N-classification at diagnosis (OR = 1.64, $p = 0.003$). AUC of the discovery dataset was 0.828 (95%CI: 0.803-0.853) on NCV. Final model applied the reserved test dataset had an AUC of 0.847.

Table 2
Model parameters (features) and their significance.

Selected Feature	Model Coefficient	Odds Ratio	P-value
Surgeon Assessment			
% tumor volume reduced after induction	1.75	5.78	<0.001
N-classification	0.496	1.64	0.0027
Selected Feature	**Model Coefficient**	**Hazard Ratio**	**P-value**
Laryngectomy-Free Survival			
% tumor volume reduced after induction	−0.543	0.58	<0.0001
Overall Survival			
Pre-chemo tumor volume	0.262	1.30	0.174
N-classification	0.393	1.48	0.039

Table 3
Model performance evaluation.

	Cross-Validation	Independent Testing
Surgeon Assessment (area under curve)	0.828 (0.803–0.853)	0.847
Laryngectomy-Free Survival (concordance-index)	0.724 (0.699–0.749)	0.721
Overall Survival (concordance-index)	0.601 (0.567–0.635)	0.552

3.5. Laryngectomy-free survival

A total of 45 patients (39.1%) underwent laryngectomy (27 patients for definitive therapy, 16 for salvage therapy, and 2 for non-oncologic reasons). Feature selection for model building identified one feature as significant, change in tumor volume (HR = 0.58, $p < 0.0001$). Averaged C-index for NCV on the discovery dataset was 0.724 (95%CI: 0.699–0.749). Final model trained applied to the reserved test dataset had a C-index of 0.721.

3.6. Overall survival

A total of 39 patients (33.9%) had died at time of analysis. Feature selection for model building selected N-classification (HR 1.48, $p = 0.04$) and pre-chemotherapy tumor dimension (HR = 1.30, $p = 0.174$), although the latter was not significant. Averaged C-index for NCV on the discovery dataset was 0.601 (95%CI 0.567–0.635). Final model applied to the reserved test dataset had a C-index of 0.552.

4. Discussion

We have previously reported excellent outcomes with bioselection in locally advanced laryngeal cancer, showing high survival rates, comparable to upfront surgery and potentially better than unselected concurrent chemoradiation [11]. Here, we investigated a non-invasive, imaging approach complementary to surgical assessment to select patients for an organ-preservation approach that may additionally predict for LFS and OS.

We found that surgeon assessment of chemotherapy response can be predicted by a volumetric CT-based tumor reduction and patient's initial N-classification, with a high C-index on the validation dataset (0.847). We hypothesize that the correlation of N-classification with surgeon assessment may be related to a visual assessment of tumor response on the external skin surface of the neck, which might bias surgeons to expect a good response in the larynx on the basis of seeing a good response in the neck. LFS can also be predicted by non-invasive techniques, with tumor reduction predicting for LFS. Finally, OS can be predicted by N-classification, which is consistent with previous literature [19,20].

The ability to predict patient outcomes based on clinical information as shown in the current study complements previous approaches. First, this may allow for wider adoption of a bioselection approach to treatment by introducing an additional objective means of evaluating chemotherapy response. Although standard courses of induction chemotherapy are given with three cycles, as noted in the introduction, efforts to shorten the overall treatment course for these patients led to institutional adoption of a single course of chemotherapy as a bioselection tool to guide treatment decision making, which has been shown to have excellent outcomes [11]. Additionally, utilization of imaging may be more accurate in determining response rates used to guide treatment selection, as seen by the discrepancy between imaging-based and surgeon-based response rates in the current study. At the University of Michigan, bioselection is a favored approach for locally advanced laryngeal cancer in patients willing to undergo either surgery or chemoradiation. This approach aids in decision-making, allowing an in-vivo assessment of tumor response to help drive therapy decisions. It also offers excellent cancer specific and overall survival rates, comparable to upfront surgery and potentially better than unselected concurrent chemoradiation [11].

Although we have previously shown good outcomes with this approach, bioselection has not been adopted by the wider community. Likely barriers to adoption include challenges of adequate in-person assessment by direct laryngoscopy by the treating otolaryngologist, which may require significant operating room and surgeon resources, time, and risks of anesthesia. Utilizing imaging-based markers of treatment in conjunction with in-office examinations multi-disciplinary care can provide additional information especially in situations of borderline response. Importantly, imaging may also allow for better assessment of endomucosal response and of tumors in which visualization is challenging, such as those with significant paraglottic or preepiglottic space involvement. This hypothesis that imaging may allow for better assessment of endomucosal changes may explain the discrepancy seen in the current study between surgeon-assessed and imaging-assessed response rates.

In situations of borderline response and T4 tumors, imaging assessment may add to surgical assessment. The current study found that discordant patients (where imaging demonstrated <50% response to induction chemotherapy but surgical assessment suggested >50% response) had higher rates of salvage laryngectomy than concordant patients, supporting the addition of volumetric imaging analysis to current multi-disciplinary paradigms in borderline response patients.

We have also shown here that imaging response is an independent predictor of LFS. This is a novel finding given challenges in prognostication for patients with locally advanced laryngeal cancer. Predicting which patients will be at risk of future laryngectomy may offer better stratification of treatment options up front; patients at high risk of salvage laryngectomy may elect to undergo surgery upfront rather than as a salvage option which has a significantly higher rate of perioperative complications [12]. Higher NLR has previously been reported to be predictive of poorer outcomes in head and neck cancers [21–24]. Here, NLR was not selected during the model-building process. Imaging-based tumor response and potentially lab evaluation after induction chemotherapy may help stratify patients in future studies.

One limitation of our study is the limited ability to predict OS, despite improved prediction of LFS. SEER data suggests that tobacco-related head and neck cancers have high rates of comorbidity and other cause mortality [25,26]. Improved prediction of OS in models that incorporate these factors in patients with locally advanced disease may offer more judicious selection of aggressive approaches in patients with poor life expectancy [27]. Additional limitations of this study include the range of years included in the study, newer scans being of higher quality than older scans. Variability in surgeon response assessment is a theoretical limitation here, although most patients were clearly dramatic responders or not, with very few in an patients close to the cut off of 50% response. In addition, these patients are a selected group with a higher number of T4 patients as compared to previous studies (for example, 43% of patients in the current study had T4 disease, as compared to only 10% on RTOG 9111 [2]) and with the exclusion of patients with a dysfunctional larynx; thus, the patients examined on the current study may not represent the general population of advanced laryngeal cancers.

Although we aimed to investigate diagnostic CT which is broadly available, the present study did not investigate advanced imaging techniques. Future research should incorporate additional advanced imaging studies as PET-CT, CT perfusion and DCE MRI which are emerging to be prognostic and predictive in head and neck cancer [28–40]. These advanced imaging techniques may offer better quality, better delineation of tumor extend, or may be complementary by allowing physiologic assessment. Findings in the current study may not extrapolate beyond standard CT-based imaging. Further incorporation of tissue-based biomarkers, including tumor-infiltrating lymphocytes which have been shown to have prognostic value [41], as well a better understanding of the mutational landscape in laryngeal cancer [42] may offer additional inputs for better predicting outcomes in patients. Importantly, a better understanding of the ability to predict outcomes including laryngectomy-free survival from imaging-based markers may offer the opportunity in the future to potential intensify or de-escalate treatment for patients based on responses.

In conclusion, volumetric CT imaging potentially offers a non-invasive and objective opportunity to evaluate response to induction chemotherapy, complementary to surgeon assessment, which may allow wider adoption of bioselection in locally advanced laryngeal cancer.

Imaging should be used alongside the gold standard of surgeon assessment, but may be particularly useful for endophytic tumors. Better understanding of discordant responses may allow for further optimization of treatment selection. Further research into the use of imaging to predict clinical outcomes is warranted.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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