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Survival Outcomes In T3 Laryngeal Cancer Based On Staging Features At Diagnosis

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by

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SURVIVAL OUTCOMES IN T3 LARYNGEAL CANCER BASED ON STAGING FEATURES AT DIAGNOSIS.

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Stage T3 laryngeal cancer is defined by the presence of vocal cord fixation and/or invasion into any of the following: pre-epiglottic space, paraglottic fat, post-cricoid space, or inner cortex of the thyroid cartilage. These cancers are usually treated with chemoradiation rather than upfront total laryngectomy. To our knowledge, no studies have directly compared differences in survival among the varied features within the T3 staging category. This study aims to determine how the presence of each of these staging features impacts overall and laryngectomy-free survival.

Patients with clinically-diagnosed T3 laryngeal squamous cell carcinoma seen at our institution between 2010-2021 were retrospectively identified. Medical record information was collected for patient demographics, tumor characteristics, treatment course, and survival. Records were reviewed with head and neck surgeons and neuroradiologists when there was uncertainty. Patients were excluded if tumor and/or treatment information was incomplete, if metastatic disease was present at diagnosis, or if they were treated with upfront laryngectomy.

For statistical analysis, the cohort was stratified in two ways: by number of T3 staging features and by type of feature. Pre-epiglottic, paraglottic, and post-cricoid space invasion

were grouped together as “soft tissue invasion”. The primary outcome was overall survival (OS), and the secondary outcome was laryngectomy-free survival (LFS, the proportion of patients alive without laryngectomy, out of all alive patients at a certain timepoint).

102 patients met inclusion criteria for analysis, who were 79.4% male (81) and were diagnosed at a mean age of 65.3 ± 11.4 years. 68.4% of patients (67) presented with a single T3 staging feature. 48.0% of patients (49) had vocal cord fixation (either alone or in combination with other features), 63.7% (65) had soft tissue invasion, and 10.8% (11) had thyroid cartilage involvement. OS was 68.6% at 2 years and 47.9% at 5 years. LFS was 74.2% at 2 years and 72.1% at 5 years.

On Kaplan-Meier survival analysis comparing different staging features, thyroid cartilage involvement had a significant impact on OS ($p<0.001$). Cox proportional hazard regression analysis showed that older age at diagnosis ($p<0.001$), higher overall cancer stage ($p=0.003$), and thyroid cartilage involvement ($p<0.001$) all had significant impacts on OS. There were no demographic or clinical features which had a significant impact on LFS, i.e. features of patients who were more likely to receive salvage laryngectomy.

Our results suggest that overall survival may be worse for patients with thyroid cartilage invasion. The difficulty of radiologically determining the degree of thyroid cartilage invasion, which distinguishes stage T3 from stage T4 laryngeal cancer, may contribute to this finding. However, the possibility that any thyroid cartilage invasion portends worse survival cannot be excluded. In order to optimize survival for patients with T3 laryngeal cancer, our findings should be further validated with larger datasets and prospective studies to assess the need for potential changes in tumor staging or treatment guidelines.

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This thesis is dedicated to my grandfather 伍声明 and my uncle 伍文政, who taught me the importance of family and hard work, and who are an ever-present reminder to recognize the humanity of my patients in all their complexities.

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INTRODUCTION

The Anatomy and Function of the Larynx

The larynx, colloquially known as the voice-box, is a critical organ in the upper aerodigestive tract (Figure 1). It contains the vocal cords, which open to allow breathing, and which produce speech by vibrating at various frequencies while air passes through them.[1] Proper function of the vocal cords and the epiglottis, as well as an intact cough reflex, are also important in preventing aspiration of food or liquids into the lungs.[2] The three anatomical regions of the larynx—supraglottis, glottis, and subglottis—have different clinical implications in the context of laryngeal cancer.[3]

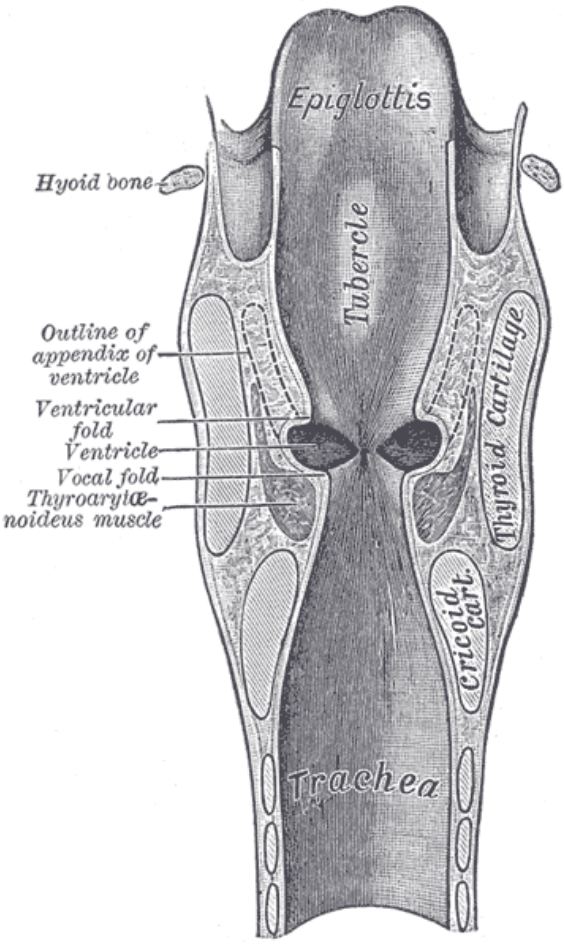


Figure 1. Coronal section of larynx and upper part of trachea. From *Anatomy of the Human Body* (1918) by Henry Gray, illustrated by Henry Vandyke Carter. Image located in the public domain.

The supraglottis is bounded by the epiglottis superiorly and the lateral angle of the laryngeal ventricle inferiorly.[3] The epiglottis is made of elastic cartilage, and covers the entrance to the larynx during swallowing. The pre-epiglottic space is found anterior to the epiglottic cartilage. Normally, the pre-epiglottic space contains fat and submucosal glands as well as lymphatics, blood vessels, and nerves extending from the supraglottis.[3] These channels also allow supraglottic laryngeal cancers to spread directly from the mucosa into the pre-epiglottic space.[4] On the other hand, the hyoepiglottic ligament, which connects the hyoid bone and the epiglottis and forms the roof of the pre-epiglottic space, serves as a barrier preventing laryngeal cancers from spreading to the base of tongue.[4]

The glottis encompasses the true vocal cords and the anterior and posterior commissures of the larynx, and its inferior border is generally considered to be one centimeter below the true vocal cords.[3] The majority of laryngeal cancers arise in the glottis.[5] Some anatomical features help to contain the local spread of glottic laryngeal cancers, such as the vocal ligament deep within the vocal cords and the conus elasticus (lateral cricothyroid ligament).[4] However, tumors may eventually invade these areas: invasion of the vocal ligament and subsequent involvement of the vocalis (thyroarytenoid) muscle leads to vocal cord fixation, and further spread into the paraglottic space allows craniocaudal spread of cancer throughout the larynx.[3,5] In addition, the location of attachment of the anterior commissure tendon on the thyroid cartilage lacks perichondrium, facilitating tumor invasion into the thyroid cartilage.[3] Interestingly, lymph node involvement is less common in glottic laryngeal cancers as opposed to supraglottic cancers, which is attributed to an inadequate submucosal lymphatic supply in the glottis.[5]

Finally, the subglottis extends from the inferior border of the glottis to the inferior border of the cricoid cartilage. It is the least common site of primary laryngeal tumor origin, but has a higher rate of extralaryngeal extension due to the rich lymphatic system in the post-cricoid space, located between the posterior aspect of the cricoid cartilage and the esophagus.[3]

The History of Laryngeal Cancer Staging

In 1959, the American Joint Committee on Cancer (AJCC) was organized for the first time to establish a standardized system to describe the extent of disease in various cancers and determine the most appropriate treatment for patients.[6] Furthermore, results of clinical studies at different institutions could be compared more reliably using a uniform system. The AJCC cancer stages were intended to be compatible with the classifications of the Union for International Cancer Control (UICC[*]), including the use of the TNM (tumor, node, metastasis) system to describe the size of primary tumors and the extent of spread to lymph nodes and distant sites.[6] Different combinations of T, N, and M stages are grouped together into overall stages, often designated with Roman numerals: for example, a patient with T3N0M0 disease and a patient with T1N1M0 disease both have Stage III laryngeal cancer.[8] Overall stage is predictive of survival and helpful in counseling patients on prognosis and determining primary treatment.[9]

In the first edition of the AJCC staging manual, published in 1977, vocal cord fixation was the only feature that defined the T3 stage for glottic and subglottic tumors.[6] For supraglottic tumors, extension to the pre-epiglottic or post-cricoid spaces or to the

[*] UICC initially stood for *Unio Internationalis Contra Cancrum* (International Union Against Cancer). In 2010, the English name was officially changed to the Union for International Cancer Control.[7]

medial wall of the pyriform sinus were also included in the T3 stage. For all subsites, T2 laryngeal cancers were those that exhibited spread to the glottis *without* vocal cord fixation, and T4 cancers were "massive" tumors extending beyond the larynx.[6]

These staging features remained unchanged until the fifth edition in 1997, which removed invasion of the medial wall of the pyriform sinus and staged it as T2, alongside other sites adjacent to the supraglottis such as the mucosa of the base of tongue and vallecula.[10] Pre-epiglottic and post-cricoid space invasion remained part of the T3 stage. In the sixth edition (2002), paraglottic space invasion was added to, or clarified as being part of, the T3 staging category.[11] In addition, the degree of cartilage invasion that distinguished T4 from T3 tumors, which had previously been vaguely described as "cartilage destruction" by "massive tumors", was finally clarified. Invasion of the inner cortex of the thyroid cartilage was explicitly defined as stage T3, and through-and-through invasion of the entire thickness of the thyroid cartilage was defined as stage T4a.[11] Stage T4b was also newly created to describe tumors extending further beyond the larynx, into structures such as the prevertebral space or the carotid artery. In the current (eighth) edition of the staging manual, published in 2018, tumor features that define the T3 stage are vocal cord fixation and/or invasion into any of the following: post-cricoid space, pre-epiglottic space, paraglottic space, or inner cortex of the thyroid cartilage.[12]

The AJCC staging system was created, and is periodically updated, through a combination of literature review, analysis of national cancer databases, and expert opinion.[6] Through this approach, consensus was achieved early on regarding the extent of disease that would define either the T2 or T4 stages. Vocal cord mobility is evidence that the tumor has not yet breached the vocal ligament and the vocalis muscle deep to it;

therefore, these tumors have a definite limited extent of spread with improved survival outcomes and are logically staged as T2.[13] On the other end of the spectrum, "massive" tumors obviously pose a significant detriment to patient outcomes, but just how "massive" a tumor must be to be staged as T4—and in particular, whether invasion into any particular structures is of comparable prognostic importance to tumor size alone—was clearly trickier to define.

Thus, with the exception of vocal cord fixation, the features of the T3 stage remained an unclear in-between category through many iterations of the staging manual. Changes in each successive edition of the AJCC staging manual reflected improved understanding of clinical outcomes for patients with these tumor features, but the result is that the T3 stage now encompasses a wide variety of features deriving from different patterns of tumor invasion throughout the larynx. In the contemporary setting, with improved treatment and surveillance techniques such as transoral laser microsurgery (TLM), intensity-modulated radiation therapy (IMRT) and narrow band imaging (NBI), it is worth revisiting the T3 staging criteria.[14-17] To our knowledge, no recent studies have directly compared outcomes between these different features that are all staged as T3 laryngeal cancer.

The Current State of Laryngeal Cancer

Laryngeal cancer is the second most common cancer of the head and neck, with 184,615 new cases and 99,840 deaths reported worldwide in 2020.[18] The disease affects four times as many males as females, and peaks in incidence at 60-70 years of age.[3,19] These cancers are almost all squamous cell carcinomas, arising from mutations in the

mucosal epithelial cells.[5] Known risk factors include tobacco and alcohol use, occupational exposures such as paint, metalworking, and construction, diets high in salt-preserved meats and fatty foods, and chronic gastric reflux.[20-24] In addition to contributing directly to oncogenic mutations in laryngeal cells, these risk factors may also influence the oral microbiome, the role of which is now increasingly being studied in head and neck cancer.[25,26]

The most common presenting symptom of laryngeal cancer is persistent hoarseness.[5] Cancers arising from the glottis, in particular, are often detected early as even small lesions can have a noticeable impact on a patient's voice quality. Other symptoms include dysphagia, odynophagia, hemoptysis, and referred otalgia.[3,5] Airway emergencies can also occur in cases of extremely advanced disease causing stridor and airway obstruction. If there is sufficient clinical suspicion, patients should be thoroughly examined by an otolaryngologist, including palpation for cervical lymphadenopathy and direct and endoscopic visualization of the oral cavity, oropharynx, and larynx.[5] Videostroboscopy can be used to assess more subtle dysfunction of the vocal cords.[5,27]

Biopsies of lesions of concern done under direct laryngoscopy in the operating room are necessary to obtain pathologic confirmation of malignancy.[5] While not included in the AJCC staging system, the degree of histological differentiation, or how similar tumor cells appear to normal cells, is also an important prognostic factor. Poorly differentiated (histologically dissimilar) tumors are more likely to metastasize than well differentiated tumors.[28] Further imaging for malignancies may include computed tomography (CT) or magnetic resonance imaging (MRI) scans of the neck and/or chest,

positron emission tomography (PET) scans, and dental X-rays to evaluate the need for dental interventions prior to treatment (e.g. removing decayed teeth).[3,5]

Given the critical functions of the larynx, striking the delicate balance between disease control and preservation of function is of utmost concern. Prior to 1991, total laryngectomy (TL) and adjuvant (postoperative) radiation was the standard of care for all patients with advanced laryngeal cancer (Stage III and IV).[29] The landmark VA Laryngeal Cancer Study demonstrated that in a high percentage of these patients, induction chemotherapy followed by definitive (curative intent) radiation could preserve the larynx without compromising overall survival.[29] Subsequently, Forastiere et al. showed that concurrent chemoradiation (CRT) improved larynx preservation compared to an induction regimen, due to a synergistic effect at the cellular level.[30] However, the benefit of CRT versus upfront TL has been shown to be less pronounced for patients with stage T4a cancer—with tumor invasion through the thyroid cartilage and/or into other adjacent structures such as the thyroid gland, trachea, tongue muscles, etc.—compared with stage T3.[31] Currently, CRT is the mainstay of treatment for patients diagnosed with T3 laryngeal cancer, while patients with stage T4a cancer are treated with upfront TL.

Due to the wide variety of staging features in T3 laryngeal cancer, there may be differences among patients staged as T3 that are less well understood. Especially in the context of de-escalation of treatment for T3 laryngeal cancer patients since 1991,[32] closer investigation of any differences between these staging features is warranted to ensure that appropriate treatment is recommended for all patients.

STATEMENT OF PURPOSE

We hypothesize that there may be differences in clinical outcomes among T3 laryngeal cancer patients that possess each of the five T3 staging features. Specifically, we aimed to determine the impact of each T3 laryngeal cancer staging feature, and combinations of multiple features, on the primary outcome of overall survival (OS) and the secondary outcome of laryngectomy-free survival (LFS).

METHODS

Cohort Inclusion and Exclusion

Data was requested from the Yale Joint Data Analytics Team (JDAT) and the Yale New Haven Hospital (YNHH) tumor registry regarding adult patients (>18 years old) with a diagnosis of laryngeal cancer seen at YNHH between 2010-2021. Specifically, the International Classification of Diseases, Tenth Revision (ICD-10) code C32 was used to search for laryngeal cancer patients within these institutional databases. JDAT also maintains records of patients who opt not to have their medical information used for research, and such patients were not included in our cohort. Using this data, patients with a clinically-diagnosed T3 (cT3) laryngeal squamous cell carcinoma were identified and included for further data collection. Given that most cT3 patients did not undergo surgery as primary (initial) treatment and thus did not have pathologic staging, inclusion of patients relied on clinical staging rather than pathologic.

Patients with incomplete tumor and/or treatment information (for example, if they received the initial diagnosis or part of their treatment at an outside hospital) were excluded from the study. Additionally, those who were restaged as T2 or T4 after

pathology analysis, or who had clinical M1 disease were excluded. Patients who received upfront total laryngectomy (TL) were included in descriptive analyses of the cohort, but excluded from survival analyses due to the known modest but significant survival benefit with surgical treatment.[31] Similarly, patients who were diagnosed with an additional primary malignancy within five years before or after their laryngeal cancer diagnosis were included in descriptive analyses and excluded from survival analyses. These clinical exclusion criteria were carefully chosen through discussion with the research team to build a representative cohort while limiting confounders. For example, patients who were initially considered to have stage T3 disease but were later determined to be T2 or T4, or vice versa, were excluded in order to limit the variability of treatment decisions made based on inaccurate initial staging.

Data Collection

Study data were collected and managed using REDCap electronic data capture tools hosted at Yale University.[33,34] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

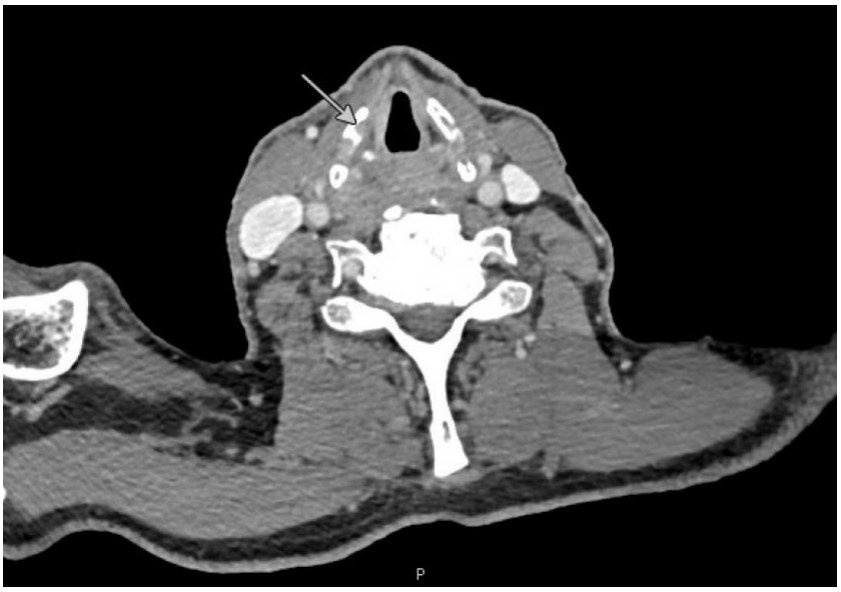
Once the patient cohort was finalized, data on these patients provided by JDAT and the tumor registry were reformatted to be directly imported into the REDCap database. Additional information was added to the database manually. Medical records

were viewed directly on Epic to collect or verify information. Specifically, most patient demographic information (e.g. race, sex), tumor characteristics (e.g. TNM stages, tumor subsite), and treatment course (e.g. chemotherapy, upfront TL) were derived from JDAT and the tumor registry. Vital status, date of last follow-up, T3 staging features, and the nature of surgical treatment were collected manually from the medical record. Information on T3 staging features could be found in clinic encounter notes, descriptions of flexible fiberoptic laryngoscopy exams performed in office, radiology reports or images, referrals placed by outside hospitals, procedure notes (e.g. for direct laryngoscopies), and/or notes from multidisciplinary tumor board discussions. The nature and intent of surgical treatment—biopsy, symptom control, or curative surgery—was determined from clinic encounter notes as well as procedure notes.

If there were discrepancies between information in JDAT or the tumor registry versus the medical record, the information in the medical record was considered to be correct or more up-to-date. When there was uncertainty within the medical record, records were reviewed with a head and neck surgeon and a neuroradiologist to ensure accuracy (Figure 2). Information was corrected manually in REDCap when necessary.

For the purposes of this study, surgical treatment was defined as a procedure intended to treat either the tumor itself or symptoms resulting from the tumor (e.g. airway obstruction). Procedures done solely for the purpose of obtaining tumor tissue samples for pathologic diagnosis were not considered surgical treatment, although they were coded as “surgery” by the tumor registry.

a)



b)

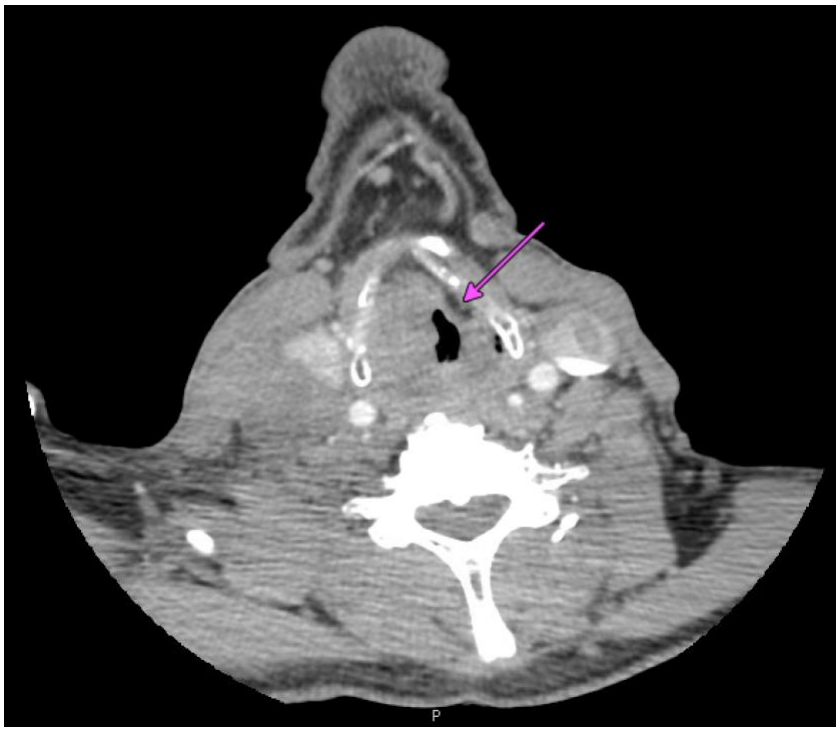


Figure 2. Images from diagnostic CT scans of patients in our cohort.

a) The existing radiologist report described “probable evidence of right thyroid cartilage involvement”. On re-review, it was determined that there was clear, albeit subtle, thyroid cartilage invasion (gray arrow).

b) The initial report did not mention the paraglottic space. On re-review, it was determined that there was effacement of the right paraglottic fat, reflective of tumor involvement. Note the normal hypoattenuation of paraglottic fat on the left (pink arrow), compared with the lack of any normal fat appearance on the right.

Additionally, patients who received cetuximab (Erbitux) were often coded as receiving "immunotherapy" by the tumor registry, as it is a drug targeting a specific receptor (epidermal growth factor receptor, or EGFR).[35] However, for this study, "immunotherapy" was specifically defined as any drug that acts on the immune system, such as pembrolizumab (Keytruda), a drug that targets PD-1 (programmed cell death protein-1) to activate an immune response against cancer cells.[36]

Statistical Methods

For statistical analysis, the cohort was stratified in two ways: by number of T3 staging features and by type of feature (Figure 3). Pre-epiglottic, paraglottic, and post-cricoid space invasion were grouped together as "soft tissue invasion", both to increase the power of our analysis as well as to reflect similarities in invasion patterns. The primary outcome was overall survival (OS), and the secondary outcome was laryngectomy-free survival (LFS, the proportion of patients alive and without laryngectomy, out of all alive patients at a certain timepoint).

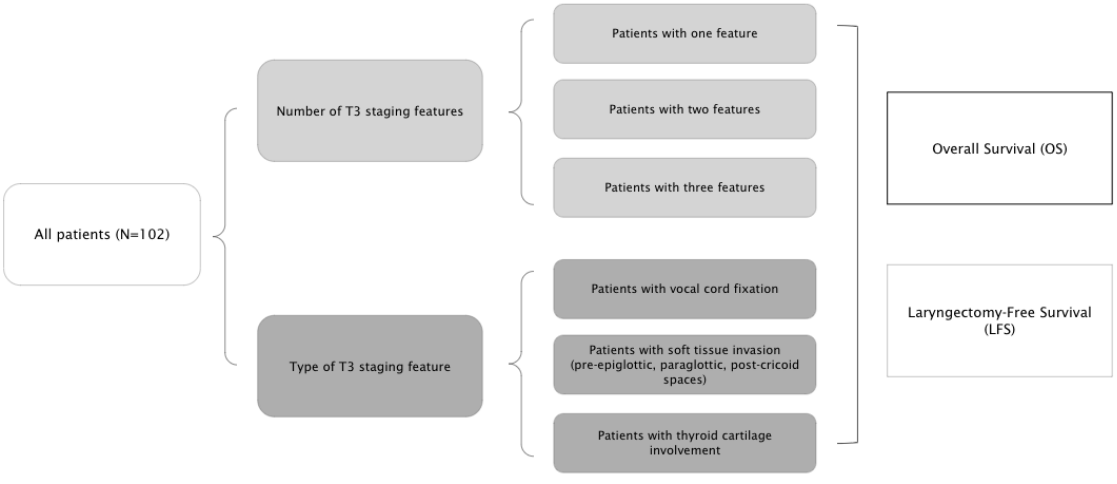


Figure 3. Schematic illustrating stratification of cohort for statistical analysis of primary outcome (overall survival) and secondary outcome (laryngectomy-free survival).

Kaplan-Meier analysis and Cox proportional hazards regression models were used for survival analysis, with significance level set at $p<0.05$. Variables entered *a priori* into the Cox regression model included the T3 staging features of interest in our study, as well as race, sex, age at diagnosis, Charlson-Deyo comorbidity index, tobacco and alcohol use history, overall AJCC stage, and recurrence given the known impact of these factors on survival.[5,31,37,38] Univariate analysis was performed to determine additional variables of potential significance to include, with significance level for this analysis set at $p<0.2$. This resulted in inclusion of insurance status and receipt of chemotherapy, radiation, immunotherapy, or total laryngectomy throughout the treatment course.

Data visualization and statistical analyses were performed using Microsoft Excel, GraphPad Prism, and R.

Ethics Statement

This study was approved by the Yale University Institutional Review Board (IRB) responsible for overseeing human subjects research under the protocol number 2000033225. Given the retrospective nature of the research posing minimal harm to patients, the study was deemed to be exempt from full IRB review. Additionally, the research team was granted a waiver of consent to access medical records for research purposes in line with the missions of Yale University and Yale New Haven Hospital as academic institutions. No information was added to or removed from the medical record, and no vulnerable populations were specifically recruited for inclusion in this study. Confidentiality of medical record information was maintained throughout the research process in accordance with ethical conduct of research guidelines.

Author Contributions

Dr. Oded Cohen and Vickie J. Wang (V.J.W.) were responsible for the initial conceptualization of the research idea and study methods. V.J.W. was responsible for drafting and submitting the IRB protocol for approval, and creating the initial patient cohort for data collection via review of information provided by JDAT and the tumor registry. V.J.W. was also responsible for creating the REDCap survey instruments necessary to record all information relevant to this study. V.J.W., with some help from Dr. Hemali Shah, was responsible for reviewing medical records in Epic to collect and verify additional clinical information. Dr. Amit Mahajan and Dr. Ansley Roche were responsible for reviewing medical records, including clinical encounter notes and CT images, in cases of uncertainty regarding staging information. Conrad Safranek was responsible for creating an algorithm to calculate Charlson-Deyo comorbidity index using ICD-9 and/or ICD-10 secondary diagnosis codes provided for each patient by the tumor registry, as well as writing a script in R to perform univariate analyses on variables of interest. Devesh Malik (D.M.) was responsible for modifying the R script for this study, and performing all statistical analyses including univariate, multivariate, and survival analyses. V.J.W. and D.M. were responsible for creating figures and tables relevant to this study. V.J.W. drafted and submitted an abstract for presentation at an international conference (see "Dissemination"), and D.M. created and presented the poster at this conference. The text of this thesis is the sole work of V.J.W. Dr. Saral Mehra oversaw all steps of the research process and has reviewed and approved this thesis.

RESULTS

Cohort Creation

Using ICD-10 code C32, which encompasses all types and stages of cancers arising in the larynx, 669 patients seen at Yale New Haven Hospital (YNHH) between 2010-2021 were identified through the Yale Joint Data Analytics Team (JDAT) and the YNHH tumor registry (Figure 4). Focusing on clinically-diagnosed T3 (cT3) laryngeal squamous cell carcinomas, 160 patients were preliminarily included for chart review. Patients with incomplete tumor and/or treatment information were excluded, as well as patients who had metastatic disease, who were ultimately determined to have T2 or T4 cancer, or who had a hypopharyngeal primary tumor.

A total of 102 patients met inclusion criteria for the final cohort. 22 patients were further excluded from survival analyses due to receipt of upfront total laryngectomy (n=5) or diagnosis of an additional primary malignancy within five years before or after their laryngeal cancer diagnosis (n=17).

Patient Demographics

Overall, the cohort was 79.4% male (81), with a mean age at diagnosis of 65.3 ± 11.4 years. Additional demographic information is displayed in Table 1 below.

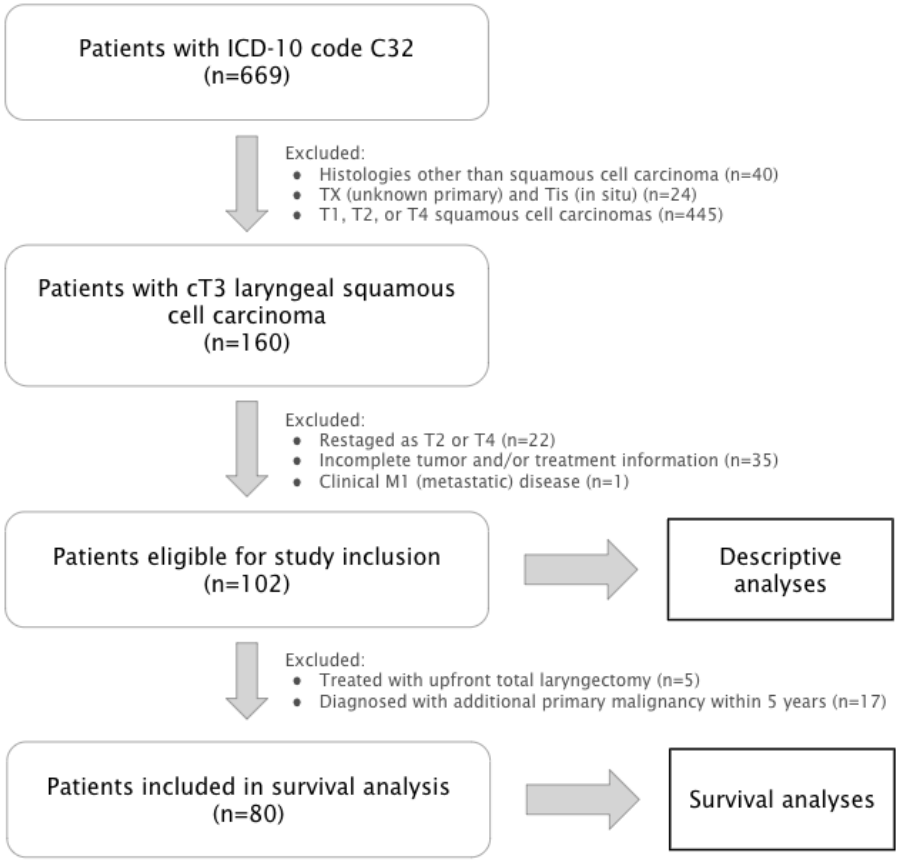


Figure 4. Schematic illustrating steps of cohort creation.

Table 1. Demographic information of patients with T3 laryngeal squamous cell carcinoma, 2010-2021.

N = 102	**n (%) or Mean ± SD**
Age (years)	65.3 ± 11.4
Sex (male)	81 (79.4%)
Race/Ethnicity	
White	79 (77.5%)
Black/African American	14 (13.7%)
Asian/Other	9 (8.8%)

Hispanic/Latino [A]	11 (10.8%)
Insurance	
Medicaid	25 (24.5%)
Medicare	48 (47.1%)
Private/managed	17 (16.7%)
Other government or Not insured	11 (10.8%)
Tobacco History	
Never used	9 (8.8%)
Ever used	93 (91.2%)
Alcohol History	
Never used	26 (25.5%)
Ever used	75 (73.6%)
Unknown	1 (1.0%)
Charlson-Deyo Comorbidity Index	
0	66 (64.7%)
1	23 (22.5%)
≥ 2	13 (12.7%)
Body Mass Index (BMI) [B]	26.7 ± 6.8

[A] Hispanic or Latino patients can be of any race in the United States census, but race was listed as "Other" for 7 of the 11 Hispanic/Latino patients in our cohort.

[B] BMI of 25.0 to 29.9 is considered to be overweight. 19 patients (18.6%) did not have height and/or weight information on file to calculate BMI.

Tumor Characteristics

The majority of patients in our cohort, about two-thirds, had Stage III disease, taking into account not only their tumor stage but also their lymph node stage. Patients commonly presented with only one T3 staging feature, though five patients in our cohort (4.9%) presented with three features. The most prevalent T3 staging feature, alone or in combination with other features, was soft tissue invasion (63.7%), including pre-epiglottic, paraglottic, and post-cricoid space invasion. Vocal cord fixation was present in nearly half of patients, and thyroid cartilage invasion in only 10.8% of patients (n=11).

Table 2. Tumor characteristics of patients with T3 laryngeal squamous cell carcinoma, 2010-2021.

N = 102	**n (%)**
Number of T3 Staging Features	
1	73 (71.6%)
2	24 (23.5%)
3	5 (4.9%)
Type of T3 Staging Feature	
Vocal cord fixation	49 (48.0%)
Soft tissue invasion	65 (63.7%)
Thyroid cartilage involvement	11 (10.8%)
Subsite	
Supraglottis	55 (53.9%)
Glottis	40 (39.2%)

Subglottis	1 (1.0%)
Not otherwise specified (NOS) or Overlapping	6 (5.9%)
N Stage	
N0	53 (52.0%)
N1	13 (12.7%)
N2 (a/b/c)	33 (32.4%)
N3 (a/b)	3 (2.9%)
Extranodal Extension	
Yes	11 (10.8%)
No (including N0 disease)	67 (65.7%)
Not evaluated or Unknown	24 (23.5%)
Overall AJCC Stage	
III	67 (65.7%)
IV (A/B/C)	35 (34.3%)
Tumor Grade/Differentiation	
Grade I: Well differentiated	11 (10.8%)
Grade II: Moderately differentiated	41 (40.2%)
Grade III: Poorly differentiated	10 (9.8%)
Grade not determined	40 (39.2%)
Additional Primary Malignancy [C]	18 (17.6%)

[C] The reader may recall that 17 patients were diagnosed with additional primary malignancies within five years before or after their laryngeal cancer diagnosis, and were

thus excluded from survival analyses. One additional patient had a remote history of malignancy and was included in survival analyses.

Demographic characteristics of patients did not differ significantly between patients with one or multiple T3 staging features, nor between patients presenting with different features.

Treatment Characteristics

Table 3. Treatment course and intent for patients with T3 laryngeal squamous cell carcinoma, 2010-2021. Percentages for sub-categories (in italics) are calculated out of the greater category above rather than the full cohort.

N = 102	**n (%)**
Surgery	**40 (39.2%)**
Primary	*10 (25.0%)*
Symptom control (tumor debulking)	*17 (42.5%)*
Salvage	*13 (32.5%)*
Chemotherapy	**86 (84.3%)**
Primary	*76 (88.4%)*
Induction	*3 (3.5%)*
Adjuvant	*2 (2.3%)*
Salvage or Palliation	*4 (4.7%)*
Radiation	**92 (90.2%)**
Primary	*81 (88.0%)*

Adjuvant	*6 (6.5%)*
Palliation or Unknown	*5 (5.4%)*
Immunotherapy	**19 (18.6%)**
Primary	*1 (5.3%)*
Adjuvant	*1 (5.3%)*
Salvage or Palliation	*17 (89.5%)*
Participation in Clinical Trial	**9 (8.8%)**

Most patients in our cohort were treated with chemotherapy (84.3%) and/or radiation (90.2%), predominantly as primary treatment. Three patients (2.9%) opted for palliative (non-curative) treatment entirely. Six patients (5.9%) were recommended chemotherapy but the regimen was not given (e.g. due to patient choice or clinical contraindication). Of the 16 patients who did not receive chemotherapy, 10 patients received radiation, either as primary treatment (n=5), adjuvant treatment following surgery (n=4), or palliative treatment (n=1). Of the 86 patients that did receive chemotherapy, 64 were treated with a single agent and 22 with multiple agents.

Of the 10 patients who underwent surgery as part of their primary treatment course, five received upfront total laryngectomy (TL), four received supraglottic (partial) laryngectomies, and one underwent local tumor excision. Of the five patients who underwent TL, only one received adjuvant chemotherapy and three received adjuvant radiation. Of the five patients who underwent supraglottic laryngectomy or local excision, three received further treatment with chemotherapy and all received radiation. Two received immunotherapy for recurrent or persistent disease, and three went on to receive salvage TL.

In total, 18 patients (17.6%) underwent TL as their first surgical procedure, and 22 (21.6%) underwent supraglottic laryngectomy (n=5), local tumor excision (n=14), or ablation (n=3). Five TLs were performed as primary treatment, as mentioned previously, and the remainder as salvage surgery for recurrent disease, persistent disease, or in one case, airway compromise following radiation treatment. Only one supraglottic laryngectomy was performed as salvage surgery for recurrent disease, and four supraglottic laryngectomies and one local tumor excision were performed as primary treatment, as mentioned previously. The remainder of supraglottic laryngectomies and local excisions were performed for the purpose of symptom control (tumor debulking) without intent to completely remove the tumor.

Survival Outcomes

Overall survival (OS) was 68.6% at 2 years and 47.9% at 5 years (Figure 5). Laryngectomy-free survival (LFS) was 74.2% at 2 years and 72.1% at 5 years. Average length of follow-up was 37.2 ± 30.0 months. Five patients (4.9%) who were alive at the time of data collection had not followed up in our hospital system for over 24 months.

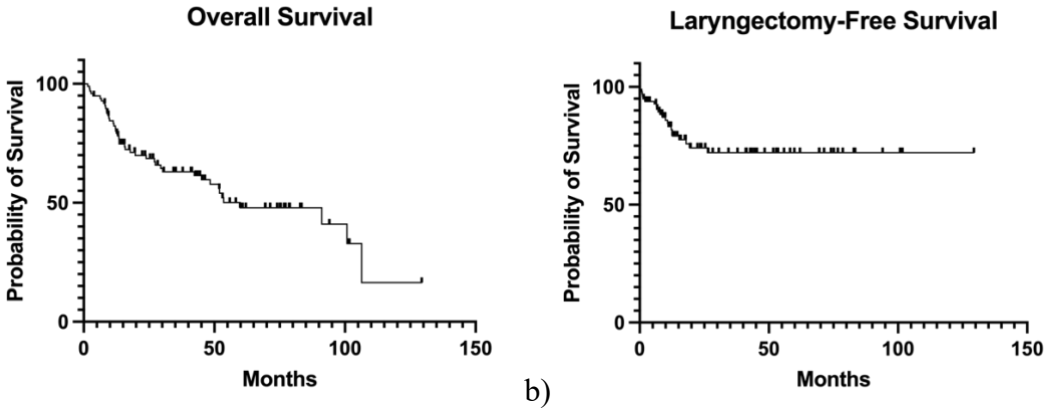


Figure 5. a) Overall survival (OS) and b) laryngectomy-free survival (LFS) for the cohort over the entire time period of follow-up.

Table 4. Survival and recurrence outcomes for patients with T3 laryngeal squamous cell carcinoma, 2010-2021. Percentages for sub-categories (in italics) are calculated out of the greater category above rather than the full cohort.

N = 102	**n (%)**
Vital Status	
Alive	54 (52.9%)
Dead	48 (47.1%)
Recurrence	
None	51 (50.0%)
Any recurrence	18 (17.6%)
Local recurrence [D]	*10 (55.6%)*
Regional recurrence	*1 (5.6%)*
Distant recurrence	*7 (38.9%)*
Never free of disease (NED)	25 (24.5%)
Unknown	8 (7.8%)
Ever had total laryngectomy (TL)	24 (23.5%)
Primary	*5 (20.8%)*
Salvage	*19 (79.2%)*
Admitted to hospice or made CMO (“comfort measures only”)	8 (7.8%)

[D] The numbers presented here describe the first location of recurrence. For example, four patients with local recurrence went on to have distant sites of recurrence.

No patients that underwent primary TL experienced recurrence or persistence of disease. No salvage TLs were performed on patients with distant recurrence. One salvage TL was aborted due to tumor involvement of the carotid artery discovered intraoperatively; however, it was considered as a salvage surgery for the purposes of analysis based on the intent of the attempt. Overall, 10 of the 24 patients (41.7%) who underwent TL at any point during their treatment course were still alive at the time of data collection.

On Kaplan-Meier survival analysis comparing different staging features, only thyroid cartilage involvement showed a significant impact on OS (p<0.001) (Figure 6). The number of staging features present at diagnosis did not impact OS.

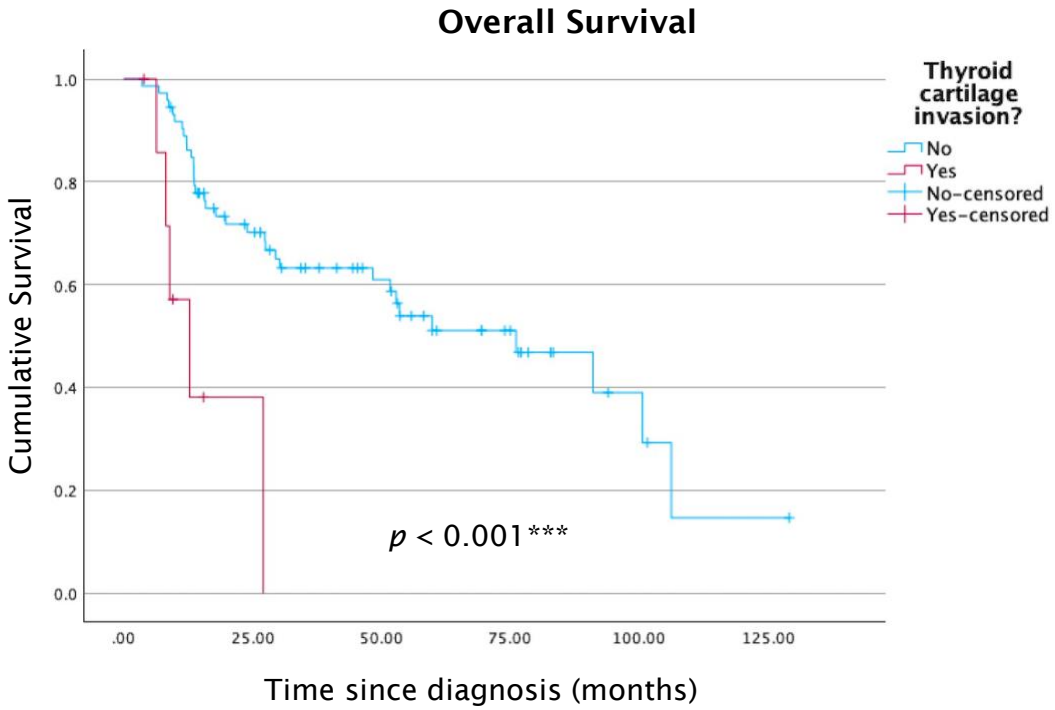


Figure 6. Kaplan-Meier survival curve for overall survival in patients with thyroid cartilage involvement.

On univariate analysis, Hispanic ethnicity, body mass index (BMI), tumor subsite, histologic differentiation, and extranodal extension did not significantly impact OS, and thus were not included in the multivariate regression model. Cox proportional hazard regression analysis confirmed the significant impact of thyroid cartilage involvement on OS (p<0.001), and additionally showed that older age at diagnosis (p<0.001) and higher overall cancer stage (p=0.003) had significant impacts on OS (Figure 7). There was a trend towards significance for Charlson-Deyo comorbidity index (CDCI) of either 0 (p=0.091) or 4 (p=0.098) when each was compared against all other indexes, with 0 being the lowest index possible. In our cohort, race, sex, tobacco or alcohol use history, insurance status, treatment type, or recurrence did not significantly impact OS.

On both Kaplan-Meier and Cox regression analysis, there were no demographic or clinical features which had a significant impact on LFS, i.e. features of patients who were more likely to receive salvage TL. This included number of T3 staging features and type of staging feature, none of which had a significant impact on LFS.

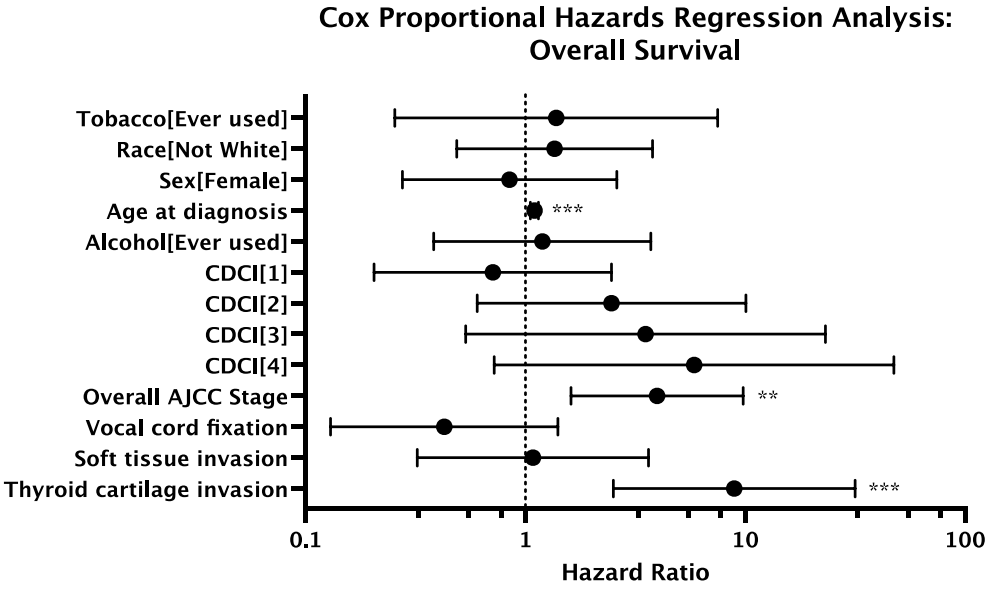


Figure 7. Cox proportional hazards regression analysis for overall survival. Significant variables described above are indicated with asterisks.

DISCUSSION

This was a retrospective cohort of 102 patients with stage T3 laryngeal squamous cell carcinoma seen over an 11-year period at a National Cancer Institute (NCI)-designated comprehensive cancer center affiliated with a large academic hospital system in the Northeastern United States. These patients were 79.4% male, 77.5% White, and on average were diagnosed at an age of 65.3 years, as expected based on the epidemiology of laryngeal cancer. The fact that almost half of patients (47.1%) were insured by Medicare at the time of diagnosis is also in line with the average age at diagnosis. Similarly, the majority of patients in our cohort had risk factors of tobacco (91.2%) or alcohol (73.6%) use. The extent of usage (e.g. pack-years) was unfortunately not systemically recorded in the medical record. The trend towards significance of the lowest and highest Charlson-Deyo comorbidity indexes (CDCI) in our cohort is corroborated by Sabin et al., who found that CDCI predicts survival when grouped into "low-" and "high-grade" morbidity categories.[37]

Interestingly, the proportion of Black patients and Medicaid-insured patients appears to be slightly higher in this cohort compared with our institution's typical patient demographic makeup, although a rigorous analysis of this observation was outside the scope of this study. Race and insurance status were not shown to have significant impacts on overall survival in our Cox regression analysis, perhaps suggesting that decreased survival rates associated with these characteristics in the laryngeal cancer literature reflect later stage at presentation rather than any quality intrinsic to the tumor or the patient. Similarly, the supraglottis was the most common subsite in our cohort, despite the fact that the most common site of origin for laryngeal cancer is the glottis. Glottic cancers

are often diagnosed in earlier stages, so the prevalence of supraglottic cancers in our cohort is likely due to the fact that only T3 cancers were included.

Almost two-thirds of our cohort had Stage III disease at diagnosis, corresponding to N0 (no lymph node metastasis) or N1 status (single ipsilateral lymph node less than 3 centimeters in diameter) in combination with T3 disease. Of those who had a positive (metastatic) lymph node, only 11 were recorded as having extranodal extension (ENE), determined either clinically or pathologically. However, many patients (23.5%) had positive lymph nodes but unknown ENE status. This is likely attributable to the fact that ENE was not recognized as a prognostic factor for overall survival in the AJCC 7th edition staging manual (2010), which was in effect when many of these patients were staged.[39] ENE has since been included in the 8th edition staging manual (2018),[12] and we anticipate that ENE will be better documented in the medical record going forward.

The majority of patients received standard of care treatment with primary chemotherapy and radiation, and overall survival and recurrence rates in our cohort were similar to national averages.[12] 27 patients (26.5%) underwent surgery as part of primary treatment, either for reasons of symptom control or due to patient or surgeon preference for surgical management. 19 patients (18.6%) received salvage total laryngectomies, almost exclusively within the first two years, when recurrence risk is highest and close follow-up is strongly recommended.[16] Patients who received immunotherapy generally received it for salvage or palliative reasons, in line with current patterns in clinical practice of prescribing immunotherapy for recurrent or persistent disease or when the patient is near the end of life.[40] Very few patients opted for palliative (non-curative) treatment only.

The key finding of our study was that thyroid cartilage involvement in patients with T3 laryngeal cancer may portend worse overall survival (OS), based on the results of both Kaplan-Meier survival analysis and Cox regression analysis. Specifically, when controlling for possible confounders on multivariate analysis including well-established prognostic factors such as age at diagnosis and overall AJCC stage, thyroid cartilage invasion was associated with a nine-fold increase in risk of death over time. No other T3 staging features, nor the presence of multiple staging features at diagnosis, were associated with an increased risk of death over time. In addition, no demographic or clinical factors were associated with an increased risk of salvage laryngectomy.

This is likely attributable, at least in part, to the difficulty of distinguishing thyroid cartilage involvement as tumor invading the inner cortex only, or invasion into or through the outer cortex which would stage the tumor as T4. Indeed, Nakayama & Brandenburg found that up to 50% of laryngeal cancers with thyroid cartilage involvement may be understaged.[41] They did not find that understaging had a significant effect on prognosis, but their study was conducted prior to the widespread adoption of larynx-preserving chemoradiation as primary treatment for T3 laryngeal cancers. Today, with different treatment recommendations for T3 and T4 laryngeal cancers, the potential consequences of understaging may be significant. Improving the accuracy of staging when there is thyroid cartilage involvement is critical. For example, some have suggested the use of MRI to better evaluate subtle thyroid cartilage involvement.[42] Additionally, there should be investigation into non-invasive novel imaging techniques or biomarkers that can help more accurately determine the degree of thyroid cartilage involvement.

Still, the possibility that *any* thyroid cartilage involvement portends worse overall survival also cannot be excluded based on our study. Historically, "minor" cartilage involvement (i.e. invasion of the inner cortex only) was deemed to have sufficiently improved survival rates compared to "cartilage destruction" that the AJCC separated these two characteristics into stage T3 and stage T4, respectively. However, we found a substantial increase in risk of death over time in our cohort, even with careful review of imaging by an experienced head and neck surgeon and neuroradiologist to resolve any uncertainties regarding tumor features. This raises a serious concern that, aside from difficulties in staging T3 versus T4 disease, tumors invading any portion of the thyroid cartilage may behave more aggressively or may not respond as well to current treatments. Indeed, Chone et al. found that even in early glottic cancers (stage T1-T2a), involvement of the anterior commissure, which is part of the anatomical pathway of thyroid cartilage invasion, was associated with greater likelihood of positive surgical margins and subsequent recurrence.[14] Our findings should be validated with larger, multi-institutional cohorts, and future studies should consider prospectively stratifying patients by staging feature to better evaluate the impact of thyroid cartilage involvement on overall survival in T3 laryngeal squamous cell carcinoma.

Challenges and Limitations

As with any research, this study is not without limitations. Primarily, the cohort was relatively small at 102 patients, and in particular there was a small number of patients (n=11) with thyroid cartilage involvement, alone or in combination with other T3 staging features. There may be a higher variability of patient characteristics or outcomes

within a small cohort compared with a larger one, which can affect the reliability of our conclusions. However, utilizing larger (e.g. national) cancer databases for this research was not possible, as they do not systematically record specific staging features which were central to our study question. Collating data from multiple institutions is certainly a reasonable next step in this research direction, although this would require more human and institutional resources than the scope of the current project allows. As it stands, this cohort does encompass virtually all T3 laryngeal cancer patients seen at a comprehensive cancer center over 11 years, and the demographic makeup and survival outcomes of the cohort correspond to national trends in laryngeal cancer. Exclusion criteria, as addressed previously, were carefully chosen to limit confounders in our cohort while maintaining statistical power.

The retrospective design also affects our ability to standardize data collection for higher quality and homogeneity. The most obvious effect is that we were unable to independently and systematically verify T3 staging features present at initial diagnosis, other than those that could be determined from the medical record (e.g. videos taken during in-office laryngoscopy or images from CT scans). Indeed, by far the most common reason for patients to be excluded from the cohort was missing information about T3 staging features. It is not known whether this could be associated with differences in the management of these patients. Other demographic and clinical characteristics potentially subject to omission or human error in data entry were similarly unable to be independently verified due to the retrospective design. Cause of death, in particular, was rarely entered into the medical record, prohibiting us from calculating disease-specific survival. To mitigate errors, data was cross-checked whenever possible,

including expert re-review of clinical encounters and imaging when there was uncertainty. Additionally, there may be variability in imaging protocols and radiology reports that we could not control for, even when done at the same institution. For example, some radiologists may prefer to use more cautious terminology when staging a cancer patient, while others may be more confident. We did not systematically collect information on CT scanning protocols, such as contrast dosage and timing. Future prospective studies would provide opportunities to address these limitations inherent to retrospective studies.

Future Research Directions

Beyond validating our main finding with larger cohorts and prospective studies, there are numerous additional directions future studies could take based on our findings and observations. The REDCap database used for this study was built not just for this research question, but also with the goal of facilitating future research through periodic maintenance of the database. Firstly, although we did not find a survival difference for patients presenting with multiple T3 staging features compared to just one, it is important to further examine the possible implications of multiple features and to classify their importance relative to each other using recursive partitioning analysis.[43] In other words, when patients present with multiple T3 staging features, which one is most predictive of the patient's prognosis?

There are certain patient demographic factors that we did not analyze in this study, including ZIP code of residence, distance traveled to the hospital where they received treatment, and fragmentation of care (that is, receiving different parts of the

treatment course at different hospitals within or outside our system). ZIP code can reflect a patient's socioeconomic status and consequences of environmental racism (e.g. disparities in access to clean water or air pollution levels), and distance traveled corresponds with ease or difficulty of accessing healthcare.[44-46] Both of these have been shown to impact a patient's overall health and cancer outcomes. In addition, a study done at our institution showed that fragmentation of care for patients with oral cavity squamous cell carcinoma was associated with worse adherence to treatment quality metrics such as positive surgical margin rate.[47] This should be discussed with patients during shared decision-making regarding treatment decisions, and should also be addressed by institutional quality improvement (QI) committees. It would be interesting for a future study to investigate the impacts of these factors on survival in T3 laryngeal cancer specifically.

With regards to treatment, we observed that a large proportion of the patients in our cohort initially treated with sub-total surgical resection (supraglottic laryngectomy or local excision) required salvage therapy and additional surgical procedures including total laryngectomy (TL). In comparison, none of the patients who received upfront TL had recurrence of their cancer. Although the numbers in our cohort are too small to draw conclusions, with only five patients in each of these two categories, these observations raise the question of how patients with T3 laryngeal cancer should be counseled regarding upfront non-curative, sub-total surgical resections, even when combined with primary chemotherapy and radiation (CRT). Many factors could be at play in this question: was radiation therapy planning done before or after initial surgical intervention? Was tumor size significantly larger in patients who required primary resection for

symptom control (e.g. airway obstruction)? Does margin status in non-curative resections significantly impact recurrence rates, as it does in curative-intent surgical treatment?[48] With such factors in mind, future studies in larger cohorts should investigate the risk of death, recurrence, and need for total laryngectomy following non-curative sub-total surgical resection combined with CRT, versus primary treatment with either upfront TL or CRT alone.

Another question that has been discussed at length in the cancer literature is that of clinical trial participation. In our cohort, only 8.8% of patients were ever enrolled in a clinical trial. Many studies have shown that enrollment in clinical trials is low and has not significantly improved over time, and there are additional barriers to enrollment among historically marginalized groups, which impacts the representativeness of the trial cohort and therefore the generalizability of the results.[49,50] Unger et al.'s meta-analysis of 8,883 cancer patients in the United States found that over half of patients receive care at institutions without active clinical trials.[49] However, even at academic centers with active trials, almost two-thirds of eligible patients choose not to enroll. Among our cohort of patients with advanced laryngeal cancer who received care at a comprehensive cancer center, the percentage that participated in clinical trials is even lower than the 15.9% average enrollment rate at academic centers demonstrated by the aforementioned meta-analysis.[49] Characteristics of patients, providers, or trial treatments that affect clinical trial enrollment at our institution or similar institutions should be further analyzed, and interventions developed in collaboration with both patients and providers to increase clinical trial enrollment among eligible patients.

Patient engagement with palliative care resources and utilization of hospice care is another important topic in the cancer literature, especially as cancer care and medical care at large has shifted towards a more collaborative, patient-centered model in recent years. Palliative care is generally defined as an interdisciplinary approach to optimizing quality of life for patients living with serious illness, which can accompany curative treatment as well as end-of-life care depending on the patient's goals.[51] On the other hand, in order to be admitted to hospice care, a patient must have a prognosis of 6 months or less and have documented deterioration of overall health and functional status.[52] In our cohort, only 7.8% of patients were admitted to hospice or made CMO (comfort measures only) based on goals-of-care (GOC) conversations. This number may not capture all patients admitted to hospice facilities outside of our hospital system, and engagement with our institution's palliative care team or GOC conversations were not systematically recorded as part of this study. Nevertheless, it is clear that more can be done to improve patient engagement with these services. Both palliative care and hospice can improve quality of life and alleviate patient and caregiver distress by reducing unwanted interventions and granting patients and caregivers a sense of autonomy and dignity amidst the complexity of a major illness.[53-55] Unfortunately, there is limited awareness of palliative care in the United States, and many studies have documented major disparities in the usage of palliative care and hospice, including disparities resulting from clinician avoidance of GOC conversations.[53,56,57] Developing community-, faith-, and hospital-based interventions is necessary to address these disparities for marginalized communities such as Asian American/Pacific Islanders, African Americans, Hispanic Americans, and sexual and gender minorities (SGM).[56-60]

Finally, returning to the central goal of balancing preservation of laryngeal function with adequate cancer treatment, an important question that should be investigated in our cohort is the functional status of the larynx in patients who did not undergo total laryngectomy (TL). Feeding tubes, such as nasogastric tubes (NGT) and percutaneous endoscopic gastrostomy tubes (PEG or G-tubes), and tracheostomy tubes are often placed in patients undergoing treatment for advanced laryngeal cancer, with the goal of removing the tube once the patient is able to maintain adequate nutrition by mouth and protect their airway.[61,62] On average, this takes 9 months for PEG tubes and 7 months for tracheostomy tubes according to Tulunay-Ugur et al., in a single-institution cohort of patients with oropharyngeal, hypopharyngeal, and laryngeal cancers treated with concurrent chemoradiation (CRT).[62] In the context of T3 laryngeal cancer, it is not known how often patients who initially present with laryngeal dysfunction are able to regain a sufficient level of function. In other words, these patients may be living with chronic G-tubes or trachs, or may eventually need a TL to avoid airway compromise. Weighing the preservation of a nonfunctional larynx against the modest but significant survival benefit of upfront surgical treatment in advanced laryngeal cancer, better understanding of realistic functional outcomes is critical so that patients and providers can make informed decisions regarding treatment and prognosis.

DISSEMINATION

This data was presented as a poster at the American Head and Neck Society (AHNS) 11th International Conference on Head and Neck Cancer in Montréal, Canada in July 2023.

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