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Survival after refusal of surgical treatment for locally advanced laryngeal cancer

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ABSTRACT

Objective: Survival of advanced laryngeal cancer is declining while the popularity of organ preservation protocols grows. This study assesses the survival impact of refusing surgical treatment for locally advanced, resectable laryngeal cancer.

Methods: Adult patients with T3 and T4a non-metastatic laryngeal squamous cell carcinoma were identified from the Surveillance, Epidemiology and End Results 18 database from 2004 to 2013. Patients were stratified based on a recommendation for extirpative surgery and the refusal of surgery. Multivariate logistic regression modeling identified variables associated with refusal. A multivariate cox proportional hazard model produced adjusted Kaplan-Meier survival curves. Survival was compared using adjusted hazard ratios (aHR) with 95% confidence intervals (CI).

Results: Of 5786 patients in the study, 2877 were recommended for surgical treatment and 138 (4.8%) refused. Refusal of surgery was associated with unmarried status (Single, odds ratio (OR) 1.79, CI 1.10–2.92), black race (OR 1.50, CI 1.00–2.22), T3 tumors (OR 1.80, CI 1.26–2.61) and N3 nodal disease (OR 3.50, CI 1.24–8.48). Compared to patients undergoing surgery, those who refused had lower 5-year cancer specific survival and increased hazard of cancer-specific mortality (aHR 1.60, CI 1.24–2.07) which resulted in decreased 5-year survival (50.0 vs 60.1%), after controlling for other factors.

Conclusion: Refusal of surgery for locally advanced laryngeal cancer is more common in patients without marital support and with T3 tumors. This decision results in a 10% survival decrease at 5-year. Future study is needed to understand patients' reasoning behind this decision and to investigate additional factors not available in this dataset.

Background

More than 13,000 new laryngeal cancer diagnoses are anticipated in the United States this year [1] and unlike other head and neck cancers, survival is worsening [2,3]. Historically, locally advanced laryngeal cancer was treated surgically, usually by total laryngectomy, followed by radiation therapy for high risk patients [4]. Alternative therapies were sought to avoid the permanent stoma and loss of natural voice inherent to laryngectomies. In the 1990s, the landmark Veteran's Affairs (VA) trial introduced organ-preservation therapy as an acceptable alternative [5]. With additional data from subsequent studies [6,7], concurrent chemoradiotherapy (CRT) became established as the preferred treatment for improved functional outcomes without sacrificing survival in appropriately selected patients [8].

However, appropriate selection of patients for CRT continues to be debated; particularly around the issues of vocal cord fixation, extent of cartilage invasion, existing organ dysfunction and tumor size [9–13]. Despite this ongoing debate in the literature, non-surgical therapy has proliferated [13–16]. This trend has overlapped with decreasing survival observed on a population level [2,15,17], leading to speculation that the inappropriate application of organ preservation therapy has contributed to the declining survival [18].

In addition to provider acceptance of organ preservation regiments, patient preference may also factor into the trend away from surgical treatment. While many studies have sought to explain the decrease in laryngeal cancer survival [2,15,19], few have investigated the role of patient preference. Yet, up to 25% of laryngeal cancer patients will accept shorter survival in order to preserve a functional voice and avoid a permanent stoma [20]. Deciding on an optimal treatment for advanced laryngeal cancer is complex, requiring the consideration of numerous patient and tumor factors [21], but ultimately the decision falls to the patient.

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Despite the burgeoning literature on laryngeal cancer outcomes, there has been no previous population-level study, to our knowledge, on the survival of patients who refuse the recommendation for surgery as initial treatment. This study aims to quantify the survival implication of refusing surgical therapy for advanced laryngeal cancer, characterize refusal trends over time and identify factors associated with patient refusal. This information may assist in understanding the decline in laryngeal cancer survival and provide evidence to inform treatment choice discussions.

Patients and methods

Study cohort

A cohort of adult patients with locally advanced laryngeal squamous cell carcinoma without prior malignant diagnoses was identified from the Surveillance, Epidemiology and End Result (SEER) 18 database from 2004 to 2013. The study period was limited to years covered by the 6th edition of the American Joint Commission on Cancer (AJCC) staging system. To capture locally advanced but potentially resectable tumors, T3 and T4a tumors without distant metastases were selected. To minimize inclusion of patients pursuing palliative therapy, only patients who received surgery and/or radiation were included. Patients with unknown staging, prior malignancies or unknown reason for no surgery were excluded (Fig. 1).

Collected data included demographics (age, sex, race, marital status, insurance, county-level poverty rate), cancer stage, subsite, year of diagnosis, treatment modality, survival and reason for no surgery. Insurance was based on the "Insurance Recode 2007" variable and recoded as Uninsured, Medicaid or Insured-Other. Sociodemographic factors were assessed by county-level median income, which is has been found to correlated best patient-level Medicare data and cancer outomes [22]. Refusal of surgery was defined by the "Reason for no cancer directed surgery" variable which also included these options: performed, refused, contraindicated, not recommended and recommended not done. This variable is specific to therapeutic surgery for the index cancer and excludes biopsies and other non-oncologic surgical procedures. The SEER coding guidelines define refusal as an explicit recommendation for surgery which is then declined by the patient. The scenario in which multiple treatment options are offered (including surgery), and the patient ultimately chooses a non-surgical option, is not considered refusal [23]. The "performed" group consists of patients undergoing extirpative surgery. The determination that surgery was "not recommended" or "contraindicated" was based on the patient's treatment team and extracted by the cancer registrars. The "recommended not done" category includes patients for whom the recommendation for surgery was documented by it was not performed without a clearly documented explanation.

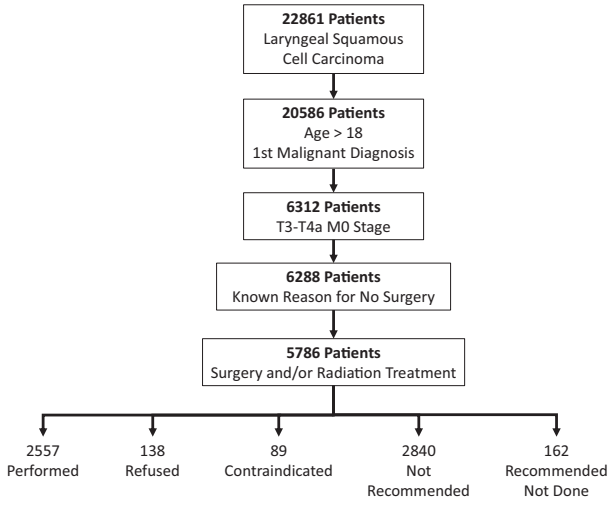

Fig. 1. Cohort selection.

The cohort is described with descriptive statistics. The patients who had surgery performed, refused surgery or in whom surgery was contraindicated were compared using chi-squared and ANOVA testing for categorical and continuous variables, respectively.

Factors associated with refusal of surgery

The characteristics of patients who refused surgery were compared to those receiving surgery using a multivariate logistic regression model. The covariates included in the model were defined *a priori* based on prior literature defining a correlation with laryngeal cancer survival. Odds ratios with 95% confidence intervals (CI) are reported. The reasons for no cancer-directed surgery were plotted as a proportion of patients by calendar year.

Survival analysis

Kaplan-Meier survival curves were created for cancer-specific survival. These curves were adjusted using a multivariate cox proportional hazard model and stratified by reason for no cancer-directed surgery. Cancer-related mortality was determined using the SEER variable "SEER cause specific death classification" which uses validated methodology to interpret cause of death based on death certificate information, primary cancer site, tumor sequence and comorbidities [24]. Survival curves were further stratified by tumor stage. Unadjusted Kaplan-Meier survival curves for each reason for no surgery were compared to patients receiving surgical treatment using log-rank testing. A multivariate cox proportional hazards model estimated adjusted hazard ratios (aHR) and 95% CI for cancer-specific mortality for the reason for no surgery while adjusting for other covariates.

Statistical analysis

Data was extracted using Seer∗Stat version 8.3.2 [25] then exported to R version 3.2.3[26] for analysis. R packages *survival*, *plyr* and *pscl* were utilized. Confidence intervals were reported at 95%. Statistical significance was set at $p < 0.05$.

Results

Cohort characteristics

The study cohort included 5786 patients, including 2857 for whom surgical treatment was recommended. The majority of the cohort was White (74.2%), male (79.8%), with T3 tumors (59.3%) (Table 1). Median follow up was 34.0 months, with shorter follow up for patients refusing surgery compared to those where surgery was performed (28.0 vs 38.0 months, $p = 0.001$). The proportion of patients refusing surgery did not show a clear trend over time and remained below 7% throughout the study period (Fig. 2). However, the proportion of patients for whom surgery was not recommended increased steadily from 40% in 2004 to 50% in 2013.

Factors associated with refusal of surgery

Relative to patients who received surgery, those who refused were more often Black (29.7% vs 22.1%, $p = 0.179$), female (24.6% vs 18.4%, $p = 0.085$), older (mean 62.6 vs 61.2 years, $p = 0.125$),