

Laryngectomy in T3 laryngeal cancer

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Abstract

Introduction

Laryngeal cancer is often managed with radiotherapy or chemoradiotherapy. This is currently the standard of care for T3 lesions. Despite this, some patients with T3 laryngeal cancer undergo surgical management in the form of total laryngectomy (TL). This study aimed to investigate indications for and outcomes from surgical management of T3 laryngeal cancers.

Methods

A retrospective cohort study of patients with T3 laryngeal cancer who underwent TL over an 11-year period.

Results

Twenty-six patients were identified. The mean age of our cohort was 60.9 years. 84.6% (n=22) were male. Borderline T4 radiological findings was the most prevalent indication for surgery (n=10, 38.5%), followed by primary radiation failure (n=7, 26.9%), bulky/airway-threatening disease (n=6, 23.1%), and a previously irradiated field (n=3, 11.5%). Oral feeding was re-established in 68% (n=17). Independent voicing was achieved in 77% (n=20) via tracheoesophageal puncture prosthesis (TEPP), TEPP and electrolarynx, or electrolarynx alone. Disease recurrence occurred in 10 (38.5%); mean time to recurrence was 7.2 months. Mean survival was 32.6 months. Mean survival was 36.4 months in the upfront surgery group and 26.4 months in the salvage group. The difference was not statistically significant (p=0.2). Feeding and speech rehabilitation rates were similar in the upfront surgery group (67% and 80% respectively) and the salvage group (70% and 89% respectively).

Conclusion

TL for T3 laryngeal cancer most often occurred where radiological ambiguity existed regarding T-staging and to salvage an irradiated larynx. Outcomes between these groups are comparable.

Introduction

Management of laryngeal cancer has changed considerably in the last 30 years following the landmark publications in the early 1990's concerning the advantages offered by primary chemoradiation in the management of locoregionally advanced laryngeal cancer¹⁻⁴. This offered multiple advantages to patients, perhaps the most important to patients being organ preservation and maintenance of voice. This is tempered with recognition of the long term speech and swallow sequelae of radiation applied to the head and neck⁵. Significantly, chemoradiation in this context demonstrated equivalent survival and locoregional control to surgery, though T-staging has long been identified as a high-risk feature predicting the risk of recurrence, failure to preserve the larynx and, ultimately, cancer related death. Recent publication has made the consequences of non-surgical management of clinically T4 lesions clear, with the 5-year disease-specific survival (DSS) of non-surgical salvage management in this setting quoted at 0% by Mimica et al⁶.

The general approach in Ireland and Europe as a whole is to prefer concurrent chemoradiotherapy in patients with T3 laryngeal lesions who are fit to receive chemotherapy⁷, and primary radiation in those who are not⁸. The general approach to T4 lesions is to offer upfront surgery in the form of total laryngectomy (TL)⁹. It is expected that a certain cohort of patients with T3 disease will undergo TL, though there is a gap in the literature as to precise indications for surgery in such cases and the outcomes thereof. Determination of indications for and outcomes from surgery in this context are of clear value to decision making.

Aims

This study aimed to determine indications for and outcomes from surgical management in a single centre cohort of patients with T3 laryngeal cancer. Specific objectives included examination of rates of recurrence, survival, and feeding and speech outcomes.

Methods

A retrospective cohort study was conducted using STROBE standardized reporting guidelines. The study cohort was derived from an existing database of patients with laryngeal cancer attending a tertiary referral centre. The database in question was constructed using hospital in-patient enquiry (HIPE) data to identify potential cases. The search strategy included the terms "total laryngectomy", "laryngectomy", "partial laryngectomy", "hemi-laryngectomy", "laryngopharyngectomy", "pharyngolaryngoesophagectomy". Cases between 2009 and 2019 were included. 172 cases were identified from the initial search strategy. Only cases with SCC as a final histological diagnosis were included, and only cases of laryngeal cancer as the primary site were included. 8 cases were excluded from analysis due to incorrect coding, leaving 116 cases for final analysis. Patients with T3 disease who underwent TL were extracted from this database for use in this study. The period of data collection was 2009-2019, with

follow-up correct and complete as of October 2021. The cohort was divided into two groups based on whether (i) surgery was the initial treatment or (ii) there was a history of therapeutic radiation either to the larynx or an adjacent field (i.e., lung, oesophagus, oropharynx, etc). These groups are hereafter referred to as the upfront surgery group and the salvage group respectively.

The primary inclusion criteria were patients with T3 laryngeal cancer (defined as pT3 on final histology as per American Joint Committee on Cancer (AJCC) 8th edition criteria¹⁰, specifically a lesion which is “limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage), and patients who underwent primary-directed surgical management in the form of TL during the study period. Exclusion criteria included patients with another synchronous head and neck cancer (HNC) and those for whom medical notes were unavailable.

The outcome variables were time to local, regional, and distant recurrence, feeding outcome, speech outcome, time to disease-specific mortality, and time to all-cause mortality. The primary exposure variable was indication for surgical management.

Descriptive variables included gender, age, histology, management of the neck, primary lesion dimensions and excision margins, and TNM classification and staging as per the 8th Edition of the AJCC staging guidelines¹⁰.

Descriptive statistics for participants’ baseline characteristics were generated. The effect of indication for surgery on feeding and speech outcomes was analysed using Fischer’s exact test. Kaplan-Meier survival analysis was conducted to test the effect of indication for surgery on survival. Hazard ratios adjusted for gender, age, and N-staging as categorical variables were generated using multivariate Cox regression analysis. Fischer’s exact test and one-way analysis of variance (ANOVA) were applied as appropriate to test for significance of differences in descriptive variables.

There were 2 patients in the bulky disease cohort who had undergone prior radiation who were included in the upfront surgery group – this was due to the primary indication for surgery in both cases being disease bulk rather than prior irradiation.

For survival statistic calculation patients who had not completed follow-up to the specified time interval were excluded from calculation of survival statistics. This only applied to the 5-year survival figure as all identified patients had completed 2 years follow-up. Statistical analyses were conducted using Stata version 16.1. Statistical significance was assumed at $p < 0.05$.

Ethical approval for this study was sought from and approved by the St. James’ Hospital-Tallaght University Hospital joint ethics committee. The lawful grounds for processing this data falls under the heading of necessity for the performance of a task carried out in the public

interest – namely, the clarification of centre specific outcomes in head and neck cancer management. The authors have no conflicts of interest to declare.

Results

Baseline characteristics

Twenty-six patients were identified. The baseline characteristics of these patients overall and by treatment group are summarised in Table 1.

The overall mean age was 60.9 years and was similar in both groups ($p=0.6$), though a larger age range was observed in the upfront surgery group (26-79 vs 50-70). 84.6% ($n=22$) were male, and there was no significant difference to gender representation between the upfront surgery and salvage groups ($p=0.5$). NO disease was found in 42.3% ($n=11$). There was no difference in N-staging between the upfront surgery and salvage groups ($p=1$). 25 (96.2%) underwent neck dissection, 19 (76%) of which were unilateral.

The most common indications for surgery overall were a suspected T4 lesion on staging imaging following discussion at MDT ($n=10$, 38.5%), followed by primary radiation failure ($n=7$, 26.9%). 23.1% ($n=6$) had bulky/airway-threatening disease. This group was comprised of 1 who presented with airway-threatening disease and 5 who were considered to have extensive/bulky disease requiring surgery. 11.5% ($n=3$) patients had previously undergone therapeutic radiotherapy to various primary lesions (cervical oesophagus, lung apex, and glottic) in the remote past, and were referred for surgery as a result.

Mean tumour size at maximum dimension on histopathological analysis was 33.2mm. The mean size of lesions in the upfront surgery group was larger (35.6mm vs 29.5mm), though the difference did not achieve statistical significance ($p=0.13$). The mean closest margin was 7.8mm, ranging from 2mm to 30mm, and again did not differ statistically between the two groups ($p=0.61$). No positive margins were noted. The mean depth of invasion was 15.3mm, and again this was higher in the upfront surgery group (18.2mm vs 10.9mm) though the difference was not statistically significant ($p=0.08$).

Survival and recurrence

Survival and recurrence statistics are presented in Table 2. Kaplan-Meier curves for overall survival (OS) and DSS of upfront surgery versus salvage are shown in Figure 1 and Figure 2. Overall 1-year, 2-year, and 5-year OS were 61.5%, 50%, and 42.9% respectively. 1-year, 2-year, and 5-year DSS were 69.5%, 59.1%, and 50% respectively. Higher survival was observed all time points in the upfront surgery group (68.8% vs 50% OS at 1 year for example). Cox multivariate regression analysis showed no statistical difference in OS (HR 1.95, $p=0.2$) or DSS (HR 1.64, $p=0.46$) between those undergoing upfront and salvage laryngectomy.

The overall recurrence rate was 38.5%. Local, regional, and distant recurrence rates were 19.2%, 34.6%, and 19.2% respectively. Recurrence rates did not differ notably between the

treatment groups, but the mean time to recurrence was shorter in the salvage group than the upfront surgery group (4.3 months vs 9.2 months). One-way ANOVA showed the difference was not statistically significant ($p=0.2$). All patients who developed recurrence died of disease – the median survival after diagnosis of recurrence was 2.8 months.

Feeding and speech

Feeding and speech outcomes by treatment group are shown in Table 3. Documentation of long term feeding outcome was unavailable for 1 patient. 65% ($n=17$) achieved sufficient oral feeding post-operatively to allow removal of their feeding tubes. The remainder remained dependant on either rigid inserted gastrostomy ($n=5$, 19%) or surgical jejunostomy ($n=3$, 12%). There was no difference in the attainment of independent feeding by treatment group ($p=0.61$).

Documentation of speech outcome was unavailable for 2 patients. 58% ($n=15$) achieved voice via trachea-oesophageal puncture prosthesis (TEPP) with or without occasional use of electrolarynx. 19% ($n=5$) achieved proficiency with electrolarynx as their primary means of voicing, while the remainder ($n=4$, 15%) did not achieve voice rehabilitation as they died shortly after their surgery. Again, there was no difference in voice rehabilitation rate between the treatment groups ($p=0.51$).

Discussion

A broad variety of indications have been described in the literature for TL in the context of T3 disease, though many remain controversial and poorly defined. A suggested list based on the published literature is described here: imaging findings suggestive of T4 disease, airway-threatening disease/non-functional larynx, large tumour volume – “bulky disease”, salvage of failed laryngeal preserving therapy/previously irradiated field.

Imaging findings consistent with T4 disease that were subsequently down-staged on pathological analysis formed the largest single group in this study, and have previously been discussed in the literature as a group – Timmermans et al described 5 of their 101 T3 lesions in their 2014 publication requiring TL, all of which were undertaken on the basis of T4 imaging¹¹. In the larynx, radiological staging usually consists of either computed tomography (CT) or magnetic resonance imaging (MRI) of the neck to allow for accurate assessment of the outer table of the thyroid cartilage and paraglottic spaces, as invasion of either of these areas results in a designation of T4 disease¹². MRI has been described in the literature as superior for detection of cartilaginous invasion, a feature which has been described in the literature as problematic in the differentiation of T3 and T4 disease. All patients in this study were discussed at our HNC MDT and yet ambiguity still existed in their final clinical T staging¹³. While this indication may at times only be made evident with the benefit of hindsight, it remains a consideration for the contemporary MDT and has been included on this basis.

There are no absolute criteria that define the non-functional larynx in the context of laryngeal cancer, but the rationale for its identification is plainly evident – organ preservation is no panacea and cannot improve the airway protective capacity of an already dysfunctional larynx¹⁴. One suggested definition for disease that fits this category is “a very destructive lesion that requires tracheostomy and enteral nutrition due to airway obstruction, larynx penetrations, and aspirations, before starting any treatment”¹⁵. A similar approach is defined in the UK national laryngeal cancer MDT guidelines¹⁶ and a national survey of Netherlands hospitals identified stridor and the ‘non-functional larynx’ as the only exceptions to the broadly held tendency to withhold TL in the T3 cohort¹⁷. Requirement for a pre-treatment tracheostomy in particular is a relevant marker of the potential for functional laryngeal failure even if organ preserving therapy is oncologically successful¹⁸.

Tumour volume or ‘bulky disease’ has here been considered separately to airway-threatening disease. While the latter shares overlap with stridor and laryngeal function, tumour volume itself can vary significantly with or without these features. The AJCC staging criteria for laryngeal cancer currently take no account of any parameter reflecting the size of the primary lesion, instead focusing on the extent of invasion of local structures¹⁰. Increasing tumour volume has long been utilised as a negative predictor of disease response to radiotherapy outside the head and neck¹⁹ and has been demonstrated to predict outcome in laryngeal cancer^{20, 21}. While there have been no studies evaluating the use of tumour volumetry in the prognostication of T3 laryngeal cancer, given the broad range of sizes observed in both T3 and T4 primary disease it seems likely that an alternative measure such as volume might better select those in whom radiotherapy is unlikely to be effective. Notably, while tumour volume was not calculated in this study, the findings that maximal single dimension did not predict survival are congruent with Ko et al, who also specifically analysed T3 laryngeal cancer²². Clearly, unidimensional measurement is a poor surrogate for volumetry.

Finally, failure of organ preserving therapy has been described throughout the literature base as an indication for laryngectomy within T3 disease. The utility of salvage surgery in the management of recurrent or persistent laryngeal cancer has been proven time and time again to be the only effective option in a cohort with poor overall life expectancy²³. In this regard it is encouraging to see concordance between the observed data and published literature; Mimica et al described a large cohort of recurrent laryngeal cancers with a 5-year DSS of 57%; for cT3 disease specifically this was reduced to 37%. This compares favourably to the 5-year disease-specific survival of 50% observed in this study⁶. Reirradiation either for recurrent disease or in a previously irradiated field is fraught with morbidity and mortality, as this confers a considerable risk of spinal cord myelopathy, carotid artery blowout syndrome, osteoradionecrosis, and death due to treatment, which has been reported to be as prevalent as 20%²⁴.

Speech outcomes were quite favourable in the presented cohort – while almost all patients underwent either a primary or secondary puncture, some did not achieve voice with the use

of their TEPP due to a variety of reasons, most commonly either failure to develop the necessary coordination for effective use or death due to disease not long after their index surgery. While some data are missing, the findings are quite comparable to a similar recently published work and indeed displays comparatively minimal attrition bias and a higher rate of voice rehabilitation²⁵. Feeding outcomes represent an equally important marker of patient autonomy that must often be sacrificed for curative treatment. Oral feeding was re-established in 68% in this study with the remaining 32% requiring percutaneous endoscopic gastrostomy or rigid inserted gastrostomy supplementation to ensure appropriate nutrition. Nutrition has been highlighted in HNC as an important area to monitor carefully due to higher rates of morbidity and mortality observed in the malnourished patient. Oral feeding rates post laryngectomy have been reported as high as 81%²⁶ and 94%²⁷, though refractory dysphagia can ultimately result in some of those for whom oral feeding was re-established becoming gastrostomy dependent.

The primary limitations of this study are the small study size and the retrospective nature of the analysis undertaken, the latter manifesting mainly in some missing speech and feeding outcome data and the difficulty in collecting more detailed parameters of the same. The sample size is a reflection of the limited number of T3 patients who are both unsuitable for organ preserving therapy and suitable for operative intervention.

Conclusion

Radiological findings suggestive of T4 disease was the most common reason for which T3 laryngeal cancer patients underwent TL. Survival, speech, and feeding outcomes are comparable between upfront and salvage TL for T3 laryngeal cancer.

Declarations of Conflicts of Interest:

None declared.

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Tables

Table 1 – Baseline characteristics of T3 laryngeal cancers requiring surgical management, 2008-2020

Variable		Upfront Surgery	Salvage	Total	p-value
Age (years)	Mean	61.75	59.5	60.9	
	Median	65	57	62.5	
	Range	26-79	50-70	26-79	0.62
Gender	Male	13 (81.3%)	9 (90%)	22 (84.6%)	
	Female	3 (18.7%)	1 (10%)	4 (15.4%)	1
Histology	SCC	16 (100%)	10 (100%)	26 (100%)	1
N Stage	0	6 (37.5%)	5 (50%)	11 (42.3%)	
	1	5 (31.25%)	3 (30%)	8 (30.8%)	
	2	4 (25%)	2 (20%)	6 (23.1%)	
	3	1 (12.5%)	0 (0%)	1 (3.8%)	1
Neck Dissection	Yes	15 (93.8%)	10 (100%)	25 (96.2%)	
	No	1 (6.2%)	0 (0%)	1 (3.8%)	0.62
Indication for surgery	Imaging concerning for T4	10 (63%)	0 (0%)	10 (38.5%)	
	Bulky/airway-threatening disease	6 (37%)	0 (0%)	6 (23.1%)	
	Radiation failure	0 (0%)	7 (70%)	7 (26.9%)	
	Prior radiation	0 (0%)	3 (30%)	3 (11.5%)	
Tumour characteristics	Size (mean)	35.6mm	29.5mm	33.2mm	0.13
	Depth (mean)	18.2mm	10.9mm	15.3mm	0.08
	Closest margin (mean)	8.3mm	7mm	7.8mm	0.61

Table 2 – Survival and recurrence statistics of T3 laryngeal cancers requiring surgical management, 2008-2020

Variable		Upfront surgery	Salvage	Total
All-cause survival	1-year survival	68.8%	50%	61.5%
	2-year survival	56.3%	40%	50%
	5-year survival	50%	33%	42.9%
Disease-specific survival	1-year survival	78.6%	55.6%	69.5%
	2-year survival	64.3%	50%	59.1%
	5-year survival	57.1%	40%	50%
Any recurrence	Recurrence rate	37.5%	40%	38.5%
	Mean time to recurrence (months)	9.2	4.3	7.2
Local recurrence	Local recurrence rate	25%	10%	19.2%
	Mean time to recurrence (months)	8	2	6.8
Regional recurrence	Regional recurrence rate	31.3%	40%	34.6%
	Mean time to recurrence (months)	9	4.2	6.9
Distant recurrence	Distant recurrence rate	18.8%	20%	19.2%
	Mean time to recurrence (months)	9.7	2.5	6.8

Table 3 – Feeding and speech outcomes of T3 laryngeal cancers requiring surgical management, 2008-2020

Variable		Upfront surgery	Salvage	Total	p-value
Feeding Outcome	Oral	10 (67%)	7 (70%)	17 (68%)	0.61
	RIG	3 (20%)	2 (20%)	5 (20%)	
	Jejunostomy	2 (13%)	1 (10%)	3 (12%)	
Speech Outcome	TEPP	8 (53%)	7 (78%)	15 (62%)	0.51
	Electrolarynx	4 (27%)	1 (11%)	5 (21%)	
	No voice rehab	3 (20%)	1 (11%)	4 (17%)	

Figure Titles

Figure 1 – Kaplan-Meier function of upfront vs salvage surgery on overall survival in T3 laryngeal cancer

Figure 2 - Kaplan-Meier function of upfront vs salvage surgery on disease-specific survival in T3 laryngeal SCC