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Decision making in advanced larynx cancer: An evidenced based review

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ABSTRACT

Organ preservation versus total laryngectomy for advanced laryngeal cancer continues to be hotly debated. This review presents evidence-based decision making points for these patents.

Background

Advanced laryngeal cancer will affect over 4500 North Americans in 2018. These cancers include those classified as T3 or T4 as well as stage III or IV. The disease and its therapy often cripple essential functions including speech, swallowing and breathing. Thus, over time oncologists have changed their mantra from "survival at all costs" to "survival with maximum functional and quality of life outcomes;" making the treatment of advanced laryngeal cancer a fine balancing act.

Treatment paradigms for advanced laryngeal cancer stem from the Veteran's Affairs Laryngeal Cancer Study (VA Study) [1], published in 1991, and the Radiation Therapy Oncology Group (RTOG) 91-11 trial published in 2003 [2]. Both studies showed promising results for organ preserving strategies which led to a shift from laryngectomy to chemoradiation (CRT) as a preferred first line treatment for advanced laryngeal cancers in academic and community centers alike. However, as population-based data began to elucidate the 'real life' scenario, the applicability of these highly controlled trials to the population at large was challenged [3]. The initial 2-year results from these trials concluded that organ preservation offered equivalent survival to primary total laryngectomy (TL), with the added benefit of an intact larynx. This strategy was widely applied to all advanced laryngeal cancers in many centers; however, large scale database studies have shown that not all advanced laryngeal cancers respond equally [4]. Moreover, the idea of "organ preservation" has been challenged as the field moves toward personalized care with careful selection of patients who are likely to retain a functional larynx [4–14].

The aim of this review is to discuss how optimal survival and functional outcomes can be achieved in advanced laryngeal cancer through appropriate patient selection.

Scoping review methods

A scoping review of the literature in the bibliographic databases in PubMed/MEDLINE was performed, focusing on advanced laryngeal cancers and outcomes including survival and laryngeal/organ preservation.

Search strategy: A scoping review was conducted using the PubMed database (1947 to present), focusing on advanced laryngeal cancers and outcomes including survival and laryngeal/organ preservation. The database was searched for English-language studies between the database start date and May 2018 using the key words *(advanced larynx/laryngeal cancer OR T3 larynx/laryngeal cancer OR T4 larynx/laryngeal cancer OR locally advanced larynx/laryngeal cancer) AND (survival OR organ preservation OR larynx/laryngeal preservation)*. The date of the last search was May 1, 2018. Before reviewing any articles, a number of techniques were used to ensure that all the relevant references were included in our search algorithm and results. Citations were cross checked (snowballing) from key publications [6,15,16], citations from existing reviews were assessed, the "related articles" to key publications in PubMed were reviewed, forward citations were used, and two experts in the field (A.E., P.D.) were consulted to make sure we were not missing any key references. A formal systematic review was not performed and is beyond the scope of this manuscript.

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Inclusion and Exclusion Criteria: We included English-language studies pertaining to patients with locally advanced larynx cancer (T3/T4) which has reported on outcomes primarily focussing on survival outcomes (overall survival given that it is the most uniformly reported). Secondarily we collected data on local control, locoregional control, disease-specific survival and disease-free survival. When reported, functional outcomes were also collected. Cohort studies, outcome studies and case series were included. Studies in languages other than English, studies pertaining to other cancer sites, reviews, commentaries, and editorials were excluded.

T3 laryngeal cancers

Perhaps the greatest controversy in the treatment of advanced laryngeal cancers revolves around T3 disease. The VA and RTOG 91-11 trials presented data showing matching survival with CRT compared to TL for all T3 disease. In 2006, Hoffman et al. performed the first data validation of the landmark trials and questioned their applicability to all advanced laryngeal cancers [4]. Their analysis of 150,000 cases from the National Cancer Database (NCDB) showed that the survival of laryngeal cancers had been down trending (68–63%) as the use of TL (19–15%) was decreasing while CRT (2–13%) was becoming the standard of care. Furthermore, they proposed that T3N0 and T3N$^+$ cancers did not have equal outcomes in terms of survival and functional laryngeal preservation.

2007 Chen and Halpern [3] analyzed over 10,000 patients in the NCDB and found that patients with T3 cancers treated with CRT had a 1.18 fold increased risk of death compared with TL ($p = 0.03$). In 2009 Olsen published a treatise on the reform of laryngeal cancer treatment [10]. He indicated that the landmark trials are likely fraught with bias: an over representation of very healthy patients, inclusion of "low volume" tumors, patient selection by overall stage and not T classification (i.e. T2s were included), and a disproportionate number of cases with mobile vocal cords. He postulated that these factors prevented the results from being widely reproduced and highlights that treatment selection should start with T classification, rather than overall stage. In a rebuttal to Olsen's paper, Wolf pointed out that the VA trial had a 5% non-significant decrease in survival in the non-surgical group. This is essentially the same difference seen in the large scale NCDB study, which was statistically significant [11]. Wolf emphasized that the landmark trials did not show treatment superiority, but only offered options for laryngeal preservation as a standard of care with TL. He also supported that not all advanced laryngeal cancers responded to CRT identically. And lastly, he pointed out that patients who responded to induction chemotherapy, where more likely to respond to definitive CRT.

In 2011, Dziegielewski et al. analyzed the Alberta Cancer Registry in Canada from 1998 to 2008 and found that T3 laryngeal cancers with paralyzed vocal cords treated with TL and post-operative RT (PORT) versus CRT had an 18% survival advantage with a hazard ratio of 2.6 [5]. The rate of long-term laryngeal preservation was 48%. 3-year locoregional control for TL + PORT was 94% versus 53% for CRT. This study certainly demonstrated that the results of the landmark trials did not apply well to all T3 cancers with paralyzed vocal cords.

Using the Surveillance, Epidemiology and End Results (SEER) database in the USA O'Neill and colleagues continued to spur the debate about T3 laryngeal cancers [17]. They isolated 300 T3 cases from 1997 to 2007 and found that 64% were treated with primary CRT and that patients treated with TL + PORT had an 18% lower risk of death. Also, this study further supported the notion that a present larynx does not necessarily equate to a functional larynx as 20% of primary CRT patients became tracheostomy tube dependent after treatment and over half needed a gastrostomy tube at some point after treatment initiation.

Al-Gilani et al. performed a parallel analysis of the SEER database and found that T3 glottic cancers treated with primary surgery have improved OS compared to those treated with CRT. One of the more important findings of this study was a 37% tracheostomy dependence rate following primary RT in patients who retained a larynx and a 31% gastrostomy tube rate [13]. Although SEER database analyses can be criticized for unintentional bias, the data does support the need for careful patient selection for organ preservation.

In 2015, a Dutch population-based study it was shown that over a 10-year period, nearly all T3 cancers were treated with organ preservation with similar survival to TL + PORT patients (52% 5 year OS) [8] However, robust conclusions could not be made due to a small sample of patients with T3 disease who received TLs.

A recent Japanese article from the radiation oncology perspective, summarized several case series of organ preservation studies over the last 20 years and demonstrated that OS has not improved with a variety of strategies. When compared to population-based studies including laryngectomy-based treatments, the survival rates differed by 5–10% in favor of TL. The authors therefore concluded that TL continues to be the oncologic gold standard [18]. However, a factor that should be kept in mind is that patients undergoing organ preservation are more likely to continue smoking and may thus, be more susceptible to cancer recurrence.

While these recent cancer registry reviews (Table 1) provide important observational data of how clinical trials have been applied and affected "real world" scenarios, they also hold faults. It is important to remember that these retrospective reviews include patients whose treatment selection criteria is unknown. For example, poor surgical candidates would have likely been treated with CRT. Luckily, this will account for a small number of patients [5].

The application of randomized controlled trials

Mariani and Pego-Fernandes have emphasized the importance of observational studies as a means of confirming the results of large scale

Table 1
Population-Based Studies - Advanced Larynx Cancer: Laryngectomy vs. Organ Preservation.

Study	Disease	N	5-yr OS CRT	5-yr OS TL	HR (95% CI)	Database
Chen et al.	Stage IV	4874	48[a]	51[a]	1.13 (1.06–1.21)	NCDB
Grover et al.	T4	969	39	50	1.31 (1.10–1.57)	NCDB
Megwalu et al.	Stage III/IV	5394	31	40	1.32 (1.22–1.43)	SEER
Dziegielewski et al.	T3/T4a	258	16	49	3.1 (1.7–5.8)	Canada
Stokes et al.	T4a	3542	38	56	1.55 (1.41–1.70)	NCDB
Harris et al.	T3/T4a	6797	NR	NR	0.79 (0.71–0.89)[b]	SEER
Timmermans et al.	T4a	3794	42	48	1.27 (1.01–1.59)	Netherlands Cancer Registry
Vengalil et al.	T4a	107	41	70	0.30 (0.14–0.61)[b]	Canada

NR: not reported; N: total sample size; OS: overall survival; CRT: radiotherapy or concurrent chemoradiotherapy; TL: total laryngectomy; HR: hazard ratio; CI: confidence interval.

[a] 4-year overall survival.

[b] Reference group was CCRT.