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Opinion

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Larynx-Preservation for T4a Laryngeal Squamous Cell Carcinoma: Where's the Evidence?

Riley P McDougall, Christopher Morrison and Jared R Robbins*

Department of Radiation Oncology, University of Arizona, College of Medicine-Tucson, Tucson AZ USA

***Corresponding author:** Jared R Robbins, Department of Radiation Oncology, University of Arizona, College of Medicine-Tucson, Tucson AZ, USA.

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For laryngeal squamous cell carcinoma, larynx preservation with maintenance of quality voice, swallowing, and respiratory functions is the hallmark endpoint of non-surgical management. However, for T4a tumors, upfront laryngectomy is the treatment of choice and prospective and randomized data on larynx-preservation outcomes in this cohort remains limited. The purpose of this short review is to evaluate the data regarding non-surgical management of T4a larynx cancers.

The sentinel VA Larynx study formed the foundation for larynx preservation treatment. The VA Larynx study randomized patients with larynx cancer to laryngectomy and post-operative radiation therapy or induction chemotherapy (3 cycles of cisplatin and fluorouracil) followed by radiation therapy for responders to chemotherapy. The study showed no difference in 2-year overall survival rates between the treatment arms, but 56% of T4 patients required a salvage laryngectomy [1].

Due to the poor outcomes for T4 tumors on the VA trial, the subsequent RTOG 91-1 trial, which randomized patients to induction cisplatin fluorouracil followed by radiation, radiotherapy with concurrent cisplatin, or to radiation alone, excluded patients with large-volume T4 disease, as defined as a tumor penetrating through the cartilage or extending more than 1cm into the base of the tongue. As a result, only 10% of the enrolled patients had T4a disease, and the specific result for this population were not reported [2].

In contrast, patients with T4 disease were included on the EORTC 24954 trial that compared chemotherapy (cisplatin with fluorouracil) followed by radiation (70Gy) against three alternating cycles of the same chemotherapy with 20Gy of radiation therapy (60Gy total). Although 30% of patients on this trial were T4, results specific to this subgroup were not reported and over 50% of patients enrolled had hypopharyngeal cancer making it difficult to draw conclusions in T4 larynx patients [3]. Likewise, data from two randomized phase II trials, the German multicenter DeLOS-II trial and the GORTEC TREMPLIN trial, provided limited evidence for larynx-preservation outcomes due to limited numbers of T4a patients (proportion of T4a: DeLOS 32%, TREMPLIN not reported) and a mix of laryngeal and hypopharyngeal cancers (proportion of hypopharyngeal tumors: DeLOS 50%, TREMPLIN 59%) [4, 5].

The remaining literature reporting laryngeal preservation outcomes for T4a tumors relies on single or small multi-institutional experiences, often using an induction or chemo-selection approach, with some being prospective protocols and others retrospective analyses [6-14]. Reported rates of larynx preservation in these studies range from 29% to 86% for chemoradiation approaches and less for RT alone techniques. In these reports the long-term tracheostomy rate was 23% to 45%, and the long-term feeding tube rate was 23% to 32%, highlighting some of the risks for aspiration, high-grade dysphagia, and airway compromise in this population [11, 15-16]. Many of these reports spanned decades and employed older radiation techniques and staging guidelines [2, 13, 14].

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As a result, the current National Comprehensive Cancer Network (NCCN) guidelines recommend upfront laryngectomy followed by pathology-directed adjuvant therapy for T4a glottic cancers. For those who are not surgical candidates or refuse laryngectomy, NCCN recommends clinical trial enrollment, radiation with concurrent systemic therapy, or induction chemotherapy [17]. For any patient with T4a larynx cancer, careful consideration should be made prior to the start of any treatment to determine the likelihood of successful larynx-preservation and quality long-term functional outcomes.

Proper patient selection is vital, as several recent reports show inferior survival outcomes for T4a patients treated with non-surgical approaches [13, 15-19]. One important selection criterion appears to the be volume of the primary tumor. Volumes less than 15cc to 21cc are associated with better outcomes, while patients with larger tumors may benefit from upfront laryngectomy followed by post-op radiation therapy with or without chemotherapy, based on final pathology [9, 10].

In general, when considering a non-surgical approach for T4a disease, multidisciplinary evaluation is critical to assess current and anticipated laryngeal function, airway management, and aspiration risks [17]. Additionally, patient's reliability of follow-up - including distance from medical facility, patient resources, and general medical care-should also be considered to ensure that any recurrent or residual disease is detected early which optimizes the chances that the recurrent disease can be successfully salvaged with a laryngectomy. Patients with limited options for follow-up may still be best served with upfront laryngectomy.

In summary, there is limited data prospective or randomized evidence reporting the outcomes of T4a larynx cancer patients managed non-operatively. As such this approach should only be offered to select patients with limited volume of disease, likelihood of good functional outcomes, those with strong support, and the ability to meet follow-up and post-treatment surveillance protocols.

Table 1: Summary of studies treating T4a Squamous Cell Carcinoma of the Larynx.

Reference	Type	Topic/objective	Arm(s)/Cohort(s)	N	Median FU	Results
Wolf, 1991 [1]	RCT	Larynx preservation	1) Induction chemo◊RT 2) Laryngectomy + post-op RT	332	33 (m)	Larynx preserved in 64% of patients, no difference in OS, cartilage invasion poor prognosis for organ preservation, 25% T4 (AJCC 1985)
Forastiere, 2003, 2013 [2]	RCT	Timing of chemo-therapy	1) Cisplatin/5FU ◊ RT 2) RT + concurrent cisplatin 3) RT alone	547	3.8 (y)	Locoregional control higher with RT+CC, Chemo improved DFS vs RT, no difference in long-term OS, high-grade toxicity higher with RT+CCRT, included small volume T4 (10%)
Rosenthal, 2015, MDACC [15]	RSI	Surgery vs LP for T4 Larynx cancer (AJCC 7th)	1) Surgery + adj. RT 2) RT +/- Chemo	221	47 (m)	Better locoregional control and functional outcomes with upfront surgery, but medial OS was similar, LP reserved for minority of patients with limited volume T4 tumors, no aspiration, tracheostomy, and limited cartilage destruction.
Popovtzer, 2016, Israel [8]	SAT	Chemo-selection	1) Induction docetaxel, cisplatin, and 5 FU ◊>50% response ◊ CRT and <50% response ◊ laryngectomy	26 (14 T4)	37.5 (m)	Response to induction chemo associated with improved 2-yr OS, all T4 cases were high volume with invasion through cartilage and had a 70% response rate.
Stenson, 2012, U Chicago [7]	RSI	Outcomes for T4 tumors	1) All had concomitant CRT +/- induction chemotherapy (treated on prospective trials)	80	4.1 (y)	69% large volume tumors, 67.7% functional-preservation, 2-yr DSS was 80.1% for group and 79.4% for large tumors with PFS of 52.6% for group and 47.6% for large tumors,
Mouw, 2012, Multi-inst [20]	MIT II	Performance and QoL for T4 tumors after CRT	Three cohorts of induction Chemo followed by CRT	25	N/A	24 of 25 patients had a complete response, QoL and performance decline during and immediately after treatment, and improve from baseline at various times after completion, many exceed pre-treatment function
Oh, 2019, BC [14]	RMI	Compared outcomes for T4a patients	1) Laryngectomy +/- adj treatment 2) CRT 3) RT alone	329	2 (y)	ChemoRT and Surgery+RT were associated with better OS compared to single modality treatment

Dziegielewski, 2012, Alberta [13]	PBS	Survival outcomes for advanced larynx cancer	1) Laryngewctomy =/- adj treatment 2) CRT 3) RT alone	258	3.4 (y)	AJCC 7 staging, Laryngectomy +/- adjuvant treatment provides superior survival compared to LP approaches
Hsin, 2013, Taiwan [10]	RSI	Prognostic value of tumor volume	1) CRT 2) Surgery	62	34 (m)	OS, PFS, Local control rate was significantly lower for tumor volume ≥15 cm^3, TL better outcomes for large tumors
Knab, 2008, U Chicago [6]	RSI	T4 outcomes after CRT	Three cohorts of induction Chemo followed by CRT	32	34 (m)	For those disease free at 1-yr, 90% had normal/understandable speech,
Shiao, 2017, MDACC [9]	RSI	Prognostic value of tumor volume	1) Laryngeal preservation 2) Laryngectomy +/- adjuvant therapy	124	48.5 (m)	5-yr OS was inferior for tumor volume ≥21cm^3 after LP, but not upfront TL, Tumor volume correlated with DSS, event-free survival, RFS, and OS
Vengalil, 2016, Princess Margaret [11]	RSI	Clinical outcomes T4, Surgery vs CRT	1) RT/CRT 2) Laryngectomy +/- adjuvant therapy	107	4.4 (y)	Larynx preservation in >2/3 patients with CRT, patients with low volume, minimal cartilage involvement had better outcomes
Worden, 2009, Michigan [12]	RSI	Chemo-selection for T4 tumors with cartilage invasion	1) Induction chemo (1 cycle cisplatin) ◊ CRT if >50% response	36	69 (m)	81% had >50% response to induction chemo with 58% laryngeal preservation rate after CRT, reasonable functional outcomes

Abbreviations: RCT: Randomized controlled Trial; SAT: Single-arm Prospective Trial; RMI: Retrospective multi-institution; RSI: Retrospective single-institution; PBS: Population-based study; 3D-CRT: Three-dimensional conformal radiation therapy; Re-RT: Reirradiation; NR: Not reported; H&N: Head and neck; OS: Overall survival; LC: Local control; HDR: High-dose rate; LR-PFS: Locoregional progression-free survival; FU: Follow-up; RT: radiation therapy; CRT: chemoradiotherapy; (m): months; (y): years

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Conflict of Interest

No Conflict of Interest.

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