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Failed larynx preservation and survival in patients with advanced larynx cancer

Cheryl C. Nocon[a,*], Jessica Yesensky[b,1], Gaurav S. Ajmani[c,2], Mihir K. Bhayani[a]

[a] Division of Otolaryngology-Head and Neck Surgery, NorthShore University HealthSystem, 2650 Ridge Avenue, Evanston, IL 60201, USA
[b] Section of Otolaryngology-Head and Neck Surgery, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, USA
[c] Pritzker School of Medicine, University of Chicago, 924 E. 57th Street, Chicago, IL 60637, USA

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ABSTRACT

Purpose: To evaluate the survival benefit of total laryngectomy (TL) after induction chemotherapy in locally advanced laryngeal cancer patients.

Materials and methods: This is a retrospective study utilizing the National Cancer Database, which captures > 80% of newly diagnosed head and neck squamous cell carcinoma cases in the United States. We included patients diagnosed with advanced stage laryngeal squamous cell carcinoma between 2004 and 2013 (n = 5649) who received either TL (n = 4113; 72.8%) or induction chemotherapy followed by either radiation therapy (n = 1431) or TL (n = 105). Kaplan-Meier curves and Cox proportional hazards regression were used to evaluate overall survival. A Cox regression model was computed to examine how the prognostic impact of treatment differed by clinical stage.

Results: In multivariable analysis, when compared to patients receiving TL alone, those receiving induction chemotherapy followed by TL experienced no significant difference in survival (HR 0.85, 95% CI 0.63–1.13), while those receiving induction chemotherapy followed by radiation experienced poorer survival (HR 1.15, 95% CI 1.06–1.26). Induction chemotherapy followed by TL was associated with improved survival compared to induction chemotherapy and radiation (P = .042). Among patients with T4a tumors, TL (P < .001) and induction chemotherapy followed by TL (P = .002) were both associated with improved survival compared to induction chemotherapy and radiation. There were no survival differences between TL and induction chemotherapy followed by TL (HR 0.76, 95% CI 0.52–1.10).

Conclusions: Larynx preservation may be attempted without compromising survival in patients with locally advanced larynx cancer who fail induction chemotherapy and undergo TL.

1. Introduction

Over 13,000 new cases of laryngeal cancer are expected in the United States in 2018, resulting in 3700 deaths [1]. The treatment paradigm for advanced-stage laryngeal cancer has shifted toward organ preservation after the Department of Veterans Affairs (VA) Laryngeal Cancer trial established organ preservation as a viable alternative to definitive surgery, or total laryngectomy (TL) [2]. The Radiation Therapy Oncology Group (RTOG) 91-11 trial demonstrated that concurrent chemoradiation (CRT) achieved higher rates of organ preservation compared to radiation therapy (RT) alone or induction chemotherapy (IC) followed by RT, without compromising survival [3]. As a result, concurrent CRT has become the dominant treatment for advanced laryngeal cancer [4].

However, the VA trial was comprised predominately of T3 disease [2], and the RTOG 91-11 excluded T4a disease [3], leading to unanswered questions regarding the optimal treatment of T4a tumors. More recent studies have evaluated outcomes for organ preservation as compared to definitive surgery in T4a disease and found improved survival with TL [4–6].

With the lack of level 1 evidence supporting larynx preservation in T4a tumors, National Comprehensive Cancer Network (NCCN) guidelines recommend definitive surgery [7]. However, within the guidelines, select patients with T4a tumors who decline surgery can select

* Corresponding author.
E-mail addresses: cnocon@northshore.org (C.C. Nocon), jayesensky@ucdavis.edu (J. Yesensky), gajmani@uchicago.edu (G.S. Ajmani), mbhayani@northshore.org (M.K. Bhayani).
[1] Present address: Department of Otolaryngology, University of California-Davis, 2521 Stockton Blvd #5, Sacramento, CA 95817.
[2] Present address: Department of Medicine, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, USA.

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organ preservation as an option. One larynx-sparing protocol recommends IC with additional management based on response: RT if complete or partial response (IC-RT, NCCN category 1 recommendation) and TL if no response or disease progression (IC-surgery). IC is also a treatment pathway option for most T3 tumors. Although the VA trial showed no survival difference between definitive surgery and IC-surgery, and two retrospective studies [8,9] showed no survival difference between IC-RT and IC-surgery, there have been no large national dataset analyses of the survival impact of failing IC for advanced laryngeal cancer.

This study examines the outcomes of patients receiving IC and progressing to either RT or TL, and those receiving definitive surgery upfront for locally advanced laryngeal cancer. The purpose of this study is to determine if there was any negative impact on survival in patients that attempt and fail laryngeal preservation with IC

2. Methods

2.1. Data source

We used data from the larynx participant user file of the National Cancer Database (NCDB), a joint project of the American Cancer Society and the American College of Surgeons Commission on Cancer (CoC). It captures > 80% of newly diagnosed head and neck squamous cell carcinoma cases from approximately 1500 CoC-accredited facilities around the United States [10]. The NorthShore University HealthSystem Institutional Review Board granted this study exempt status, and patient informed consent was waived as the study was retrospective and data from the NCDB were de-identified.

2.2. Study cohort

We identified patients diagnosed with invasive squamous cell carcinoma of the larynx from 2004 to 2013 who received either definitive surgery or induction chemotherapy followed by radiation therapy (IC-RT) or TL (IC-surgery). The NCDB records data regarding the timing of treatment, allowing us to categorize patients according to their sequential treatment. NCCN guidelines include treatment pathways with induction chemotherapy for T3/N0-1, T3/N2-3, and T4a/N0-3 tumors, thus, our analysis was restricted to patients with these stages. Staging was based on American Joint Committee on Cancer (AJCC) 7th edition criteria [11] for tumors diagnosed 2010–2013 and AJCC 6th edition criteria [12] for tumors diagnosed 2004–2009. We further excluded those with missing survival data, those diagnosed with other invasive malignancies, those receiving care at facilities other than the diagnosing facility, and those with grade 4 tumors, as these patients are more likely to have aggressive disease and an overall poorer prognosis. We identified and excluded patients who received concurrent CRT, defined as those who received chemotherapy and radiation within 7 days of each other.

2.3. Statistical analysis

Demographic and clinical characteristics between treatment groups (definitive surgery, IC-RT, IC-surgery) were compared using one-way ANOVA and chi-square tests.

The primary outcome of interest was overall survival. Kaplan-Meier curves with log-rank tests were used to compare unadjusted survival between treatment groups both overall and stratified by clinical stage (T3/N0-1, T3/N2-3, T4a/N0-3). Multivariable survival analysis was performed using Cox proportional hazards regression with treatment group, adjusting for age, sex, race/ethnicity, insurance, socioeconomic status, Charlson-Deyo comorbidity score [13], tumor subsite (glottis, supraglottis, other/unspecified larynx), tumor grade, and clinical stage. Finally, an additional Cox regression model was computed including an interaction term between treatment group and clinical stage, to examine how the prognostic impact of treatment may differ by clinical stage.

All analysis was performed using Stata 14.2 [14]. All tests were two-sided, and $P < .05$ was considered statistically significant.

Table 1
Cohort demographic and clinical characteristics, stratified by treatment pathway (N = 5649). P values from corresponding one-way ANOVA or chi-square tests. IC = induction chemotherapy. RT = radiation therapy.

	Definitive surgery (n = 4113)	IC to surgery (n = 105)	IC to RT (n = 1431)	P value
Age (mean, yrs)	60.4	56.8	58.8	< 0.001
Sex				< 0.001
Male	81.1	86.7	76.6	
Female	18.9	13.3	23.4	
Race/ethnicity				0.382
White	72.7	73.3	70.8	
Black	18.5	16.2	20.5	
Hispanic	5.8	6.7	6.4	
Other/unknown	3.0	3.8	2.3	
Socioeconomic status				0.028
Low	53.1	57.1	50.2	
Middle	30.4	32.4	30.2	
High	16.5	10.5	19.6	
Comorbidity index				< 0.001
0	63.2	64.8	70.2	
1	27.6	29.5	22.6	
≥2	9.2	5.7	7.3	
Primary subsite				< 0.001
Glottis	32.8	22.9	22.2	
Supraglottis	36.8	39.0	57.7	
Other/NOS	30.4	38.1	20.2	
Grade				0.018
1	8.7	6.7	11.3	
2	64.8	72.4	61.8	
3	26.4	21.0	26.9	
Clinical stage				< 0.001
T3, N0-1	34.5	25.7	39.3	
T3, N2-3	11.3	11.4	27.7	
T4a, N0-3	54.2	62.9	33.0	

3. Results

We identified 5649 patients meeting selection criteria. The majority were treated with definitive surgery (n = 4113; 72.8%), with fewer patients receiving IC-RT (n = 1431; 25.3%) or receiving IC-surgery (n = 105; 1.9%).

Demographic and clinical characteristics for the cohort are presented in Table 1, stratified by treatment regimen. There were significant differences between the 3 groups for all characteristics except patient race/ethnicity. Patients receiving IC, particularly those with subsequent TL, were on average younger than those with definitive surgery (IC-surgery 56.8, IC-RT 58.8, definitive surgery 60.4; $P < .001$) and had less comorbidity (Comorbidity index 0: 64.8%, 70.2, 63.2%, respectively; $P < .001$). Those treated with definitive surgery were more likely than those receiving IC to have glottis tumors (IC-surgery 22.9%, IC-RT 22.2%, definitive surgery 32.8%; $P < .001$). IC-RT patients were more likely to have supraglottis tumors (IC-surgery 39.0%, IC-RT 57.7%, definitive surgery 36.8%, $P < .001$), while IC-surgery patients were relatively more likely to have tumors elsewhere in the larynx or in an unspecified larynx sub-site (IC-surgery 38.1%, IC-RT 20.2%, definitive surgery 30.4%, $P < .001$). Patients receiving IC-surgery tended to have more T4a tumors (62.9%) than those receiving IC-RT (33.0%) or definitive surgery (54.2%, $P < .001$).

3.1. Unadjusted survival by treatment group

There were no survival differences between the 3 treatment groups

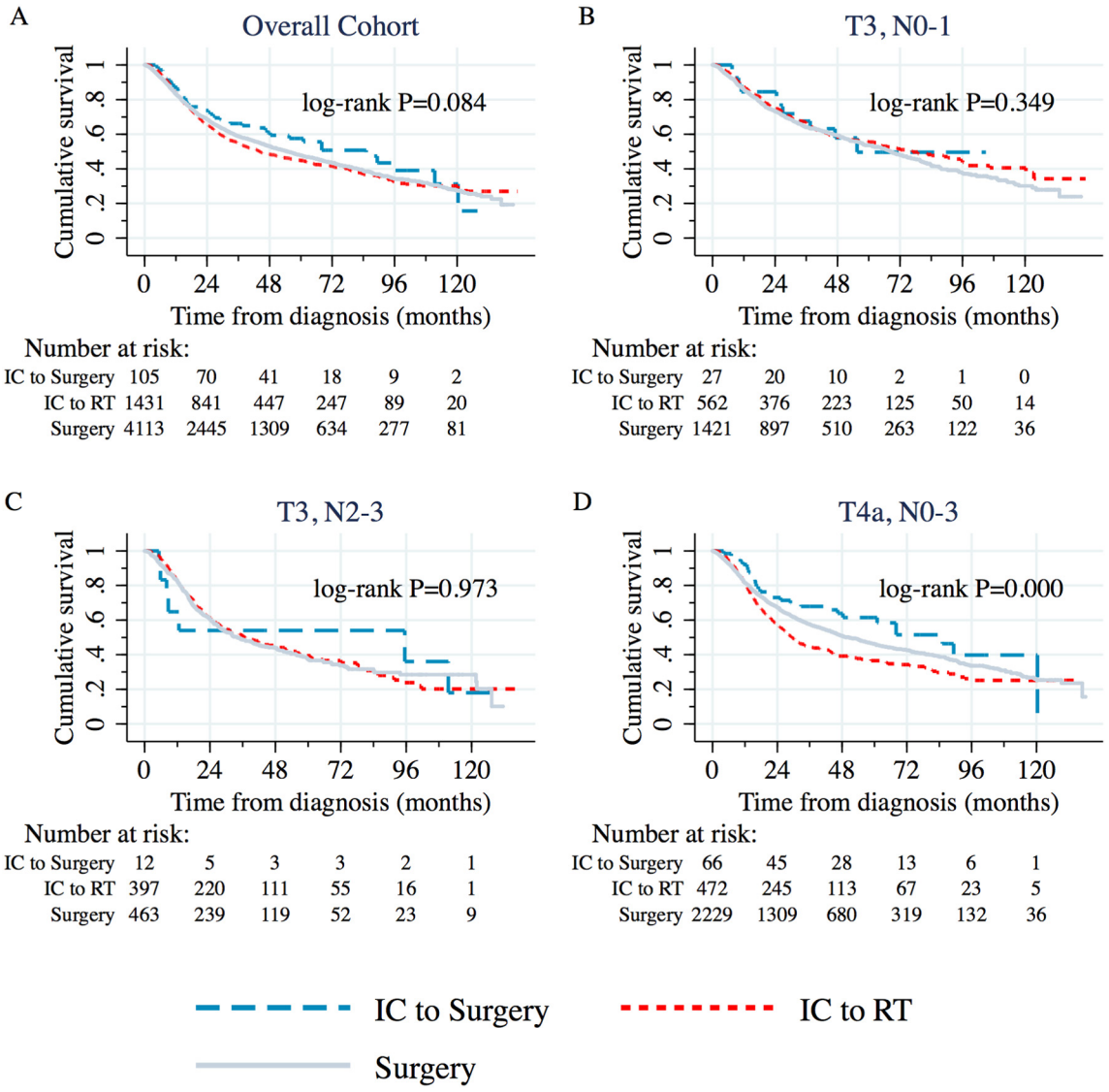

Fig. 1. Kaplan-Meier curves for overall survival for patients receiving IC-surgery, IC-RT, and definitive surgery alone. Results presented overall (A) and according to clinical stage (B–D). P values from corresponding log-rank tests.

(Fig. 1A). When stratifying by the T classification, it appeared that there were no survival differences for T3 tumors, regardless of N status. For T4a tumors, however, it appeared that patients receiving IC-RT experienced poorer survival compared to those receiving IC-surgery (P = .004) or definitive surgery (P < .001). In contrast, there was no survival difference between IC-surgery and definitive surgery (P = .101).

3.2. Adjusted survival by treatment group

In multivariable survival analysis, we found that, compared to patients receiving definitive surgery, those receiving IC-surgery experienced no significant difference in survival (HR 0.85, 95% CI 0.63–1.13), while those receiving IC-RT experienced poorer survival (HR 1.15, 95% CI 1.06–1.26) (Table 2). IC-surgery was also associated with improved survival compared to IC-RT (P = .042).

When adding an interaction term between treatment and stage to our multivariable model, allowing the association between treatment and survival to differ by stage, we found similar trends to unadjusted analysis (Table 3). For T3 tumors, regardless of N status, there were no significant differences in survival between the 3 treatment groups (P > .50, all). Among patients with T4a tumors, IC-surgery (P = .002) and definitive surgery (P < .001) were both associated with improved survival compared to IC-RT. As with univariable analysis, there were no survival differences between IC-surgery and definitive surgery for T4a tumors (HR 0.76, 95% CI 0.52–1.10).

4. Discussion

Treatment for stage III and IVA laryngeal tumors has shifted toward organ preservation ever since the first randomized trials on larynx preservation were conducted over 25 years ago. Recent national dataset analyses have demonstrated that organ preservation remains the mainstay of treatment in resectable advanced non-metastatic laryngeal cancers [4,15]. This shift has occurred despite no clear evidence for its use in T4a tumors. Because the VA trial [2] and RTOG 91-11 [3] had low rates of T4a disease, making up 26% and 10% of the study populations respectively, optimal treatment for T4a disease has yet to be established.

Despite guidelines advocating definitive surgery for T4a tumors [7], many patients are unwilling to undergo surgery and instead pursue larynx preservation strategies. TL has an obvious major impact on laryngeal function and can lead to a poorer quality of life, affecting areas of physical, emotional and social functioning [16]. It is widely

Table 2
Multivariable Cox proportional hazards survival model.

Characteristic	HR	95% CI
Treatment pathway		
Definitive surgery	Ref	
IC to surgery	0.85	(0.63, 1.13)
IC to RT	1.15	(1.06, 1.26)
Age (per year)	1.03	(1.02, 1.03)
Sex		
Male	Ref	
Female	0.81	(0.74, 0.89)
Race/ethnicity		
White	Ref	
Black	1.11	(1.01, 1.22)
Hispanic	0.81	(0.68, 0.97)
Other/unknown	0.76	(0.59, 0.97)
Insurance		
Private	Ref	
Medicare/other govt	1.22	(1.10, 1.35)
Medicaid	1.35	(1.21, 1.51)
Uninsured/unknown	1.18	(1.03, 1.35)
Socioeconomic status		
Low	Ref	
Middle	0.87	(0.80, 0.95)
High	0.88	(0.79, 0.98)
Charlson comorbidity score		
0	Ref	
1	1.09	(1.00, 1.19)
≥2	1.50	(1.32, 1.69)
Primary site		
Glottis	Ref	
Supraglottis	1.12	(1.02, 1.23)
Other/NOS	1.23	(1.11, 1.35)
Tumor grade		
1	Ref	
2	1.32	(1.15, 1.52)
3	1.55	(1.34, 1.80)
Clinical stage		
T3, N0-1	Ref	
T3, N2-3	1.51	(1.35, 1.69)
T4a	1.34	(1.23, 1.46)
Observations	5649	

Table 3
Multivariable Cox proportional hazards survival model including interaction between treatment pathway and tumor clinical stage. Other covariates in model omitted.

	T3, N0-1		T3, N2-3		T4a	
	HR	95% CI	HR	95% CI	HR	95% CI
Definitive surgery	Ref		Ref		Ref	
IC to surgery	1.09	(0.60, 1.98)	1.07	(0.51, 2.28)	0.76	(0.52, 1.10)
IC to RT	0.97	(0.84, 1.12)	1.06	(0.89, 1.27)	1.41	(1.24, 1.61)

	Overall	T3, N0-1	T3, N2-3	T4a, NX
IC_S v S	0.042	0.703	0.980	0.002
IC_S v IC_R	0.261	0.776	0.856	0.143
IC_R v S	0.002	0.680	0.507	< 0.001

accepted, however, that TL produces higher rates of local tumor control in these patients. In fact, recent studies have compared survival trends between patients receiving surgical and organ preserving approaches and found superior outcomes with definitive surgery over non-surgical therapies [4–6,15,17].

Despite attempts to save the larynx, select patients will fail or not tolerate non-surgical treatment and subsequently progress to salvage laryngectomy. We wanted to investigate the impact on survival of attempting preservation with IC followed by surgical salvage, as compared to definitive surgery and to IC followed by RT. We evaluated overall survival in T3 and T4a tumors and found no significant difference between the three treatment groups. When looking at T status independently, we again saw no difference in overall survival between patients receiving IC-surgery and those receiving definitive surgery. This is in contrast to T4a patients receiving IC-RT, who experienced poorer overall survival. Therefore, patients who attempt and fail organ preservation with IC are safely able to undergo salvage laryngectomy without negatively affecting survival.

Our study also contributes to the growing body of evidence that IC response provides important prognostic information, outcome prediction and treatment selection in patients with advanced laryngeal cancer. Patients that do not adequately respond to IC have been shown to have poorer responses to subsequent RT or CRT [2,8,9,18,19]. The speed of tumor response to IC has been shown to be an important prognostic factor and that successful organ preservation can be predicted based on response to a single cycle of chemotherapy [19]. Subset analysis of the VA trial identified a relationship between the degree of response to IC and survival, with complete responders demonstrating significantly better overall disease-free survival than partial responders [20]. Similar findings have been replicated in retrospective studies [8,9]. They have also shown that nonresponders who undergo salvage surgery have no survival difference compared to the complete responders. Our findings, in corroboration with these previous studies, demonstrate how IC response can guide treatment selection and underscore the importance of timely surgical salvage in T4a patients who do not respond to IC. Patients need to be counseled on the need for salvage TL if they do not achieve a complete response to avoid compromising survival outcomes.

Finally, there is conflicting data regarding the effect of IC on the development of distant metastasis, but two recent meta-analyses of randomized controlled trials on resectable locally advanced head and neck squamous cell carcinoma in general, and laryngeal carcinoma in particular, demonstrated a benefit of IC in the reduction of distant metastasis [21,22]. While the role of IC in this capacity is still controversial, such findings highlight the need for further research into how IC fits into our current treatment schemas.

Comparison of laryngeal preservation to definitive surgery using the NCDB has been done in a recently published study by Stokes et al. [17]. This group compared survival outcomes between definitive surgery, IC-RT, and concurrent CRT in T4 larynx cancers. They found a significant improvement in overall survival among patients treated with IC-RT compared with those treated with concurrent CRT. They also demonstrated no survival difference between patients undergoing definitive surgery and those undergoing IC-RT. However, this study did not include a cohort of patients who received IC and proceeded to surgery in their analysis, to determine if there are survival differences between IC-RT and IC-surgery. In another NCDB study, Grover et al. [4] found that nonsurgical treatment of T4a tumors produced inferior overall survival compared to TL, but their study did not differentiate between IC-RT and concurrent CRT. These results require prospective validations, but they suggest a survival advantage of both definitive surgery and IC over concurrent CRT in T4a cancers. In contrast to these previously published analyses, our study found that patients with T4a tumors who underwent IC-RT had worse overall survival compared to definitive surgery or IC-surgery. Our study findings add to the ongoing debate surrounding the role of IC in T4 larynx cancers, but it also suggests the need for future neoadjuvant trials with a surgical treatment arm to better define optimal treatment approaches.

We acknowledge the inherent limitations using information from a database. There is no information regarding the specific chemotherapy agents, dose, number of cycles, duration, and whether IC was followed by RT or concurrent CRT. Without a standardized induction regimen we cannot accurately determine the ideal time course from induction to surgery without affecting survival. The reason for progressing to surgical salvage is also unknown. Patients may have had progression of tumor, poor response or simply could not tolerate systemic therapy. If

patients with partial responses tended to get definitive surgery over radiation, leaving only complete responders to receive radiation, we may overestimate the survival benefit. Conversely, we are unable to assess whether our IC-RT cohort includes patients who refused salvage surgery after a poor response to IC, which would negatively impact survival. Additionally, there is no information regarding means of tumor assessment to determine IC response.

5. Conclusions

The optimal nonsurgical treatment approach for advanced laryngeal cancers has not yet been clearly defined. The results of our study suggest that larynx preservation may be attempted without compromising survival if patients who fail IC undergo definitive surgery. Our findings also contribute to the limited body of evidence for patients with T4a disease who elect to undergo larynx preservation, with patients who undergo IC-RT experiencing worse overall survival than either definitive surgery or IC-surgery. Such findings highlight the need for a neoadjuvant trial with a surgical option to refine management strategies for T4a tumors.

Declaration of interests

None.

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