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ORIGINAL RESEARCH

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Primary radiation therapy for advanced-stage laryngeal cancer: A laryngo-esophageal dysfunction disease-free survival

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Abstract

Objectives: To evaluate the outcomes of advanced-stage laryngeal squamous cell carcinoma (SCC) patients treated with functional-preservation strategy with a specific focus on laryngo-esophageal dysfunction disease-free survival (LEDDFS).

Methods and materials: A retrospective review was conducted of stage III-IVB laryngeal SCC patients who were treated with curative-intent radiotherapy (RT) (2007–2018). Patients were preferentially managed with upfront chemoradiation (CCRT); except for those with cN2-3, cT4, or large volume cT3 (induction chemotherapy followed by RT or CCRT is an option), and those who were unfit or declined chemotherapy (received altered RT). The primary endpoint was 3-year LEDDFS, and secondary endpoints were 3-year local failure (LF), regional failure (RF), distant metastasis (DM), overall survival (OS), disease-free survival (DFS), and acute and late toxicities. Cox proportional hazard tests were used for multivariable analysis (MVA).

Results: A total of 213 cases were included. With a median follow-up of 37 months, the 3-year LEDDFS was 50%, while the 3-year OS, DFS, LF, RF, and DM were 81%, 74%, 9%, 5%, and 7%, respectively. On MVA, cT4-category was the only predictor of inferior LEDDFS (HR: 0.47, [95% CI: 0.29–0.74], $p < .01$). The most common grade ≥ 3 acute and late radiation therapy oncology group (RTOG) toxicity were esophageal toxicity: 16.7% and 29.6%, respectively.

Conclusions: Primary RT resulted in favorable oncologic and functional outcomes in only half of the advanced-stage laryngeal cancer patients. Future clinical trials are required to investigate further treatment options aiming to improve the oncologic and maintain functional outcomes with utilization of LEDDFS as the primary endpoint.

Level of evidence: 4.

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KEYWORDS
cancer, laryngeal, laryngo-esophageal dysfunction, organ preservation, outcomes, radiation

1 | INTRODUCTION

Laryngeal squamous cell carcinoma (LSCC) is one of the most common head and neck tumors,[1,2] especially with increasing tobacco and alcohol consumption with linked association of both risk factors with the development of laryngeal cancer.[3] Treatment of locoregionally advanced LSCC is a challenging due to tumor and/or treatment-related oncologic and functional outcomes.[4–8]

Larynx-preservation approach with concurrent chemoradiation (CCRT) for the treatment of locally advanced laryngeal cancer remains a standard of care since the results of the radiation therapy oncology group (RTOG) 91–11 phase III randomized controlled trial (RCT),[9] which showed superior larynx preservation rate with treatment intensification using CCRT compared with induction chemotherapy (IC) followed by radiation therapy (RT) and over RT alone. However, overall survival (OS) was not statistically different for all three-treatment groups; because of increased non-cancer-related mortality among patients treated with CCRT.[10] This may have been partially caused by laryngo-esophageal dysfunction (LED) in the CCRT group, which is under evaluated in the majority of studies.[10–12]

In 2009, the larynx preservation clinical trial design consensus panel recommended a new endpoint: laryngo-esophageal dysfunction-free survival (LEDFS) to be the primary endpoint for future laryngeal preservation trials.[13] Events for this composite endpoint were; death, local failure (LF), total or partial laryngectomy, tracheotomy, or feeding tube dependency, however, regional failure (RF) and distant metastases (DM) were not included as events, despite that RF and DM are determinant in prognosis for laryngeal cancer patients,[14–17] and representing important events in laryngeal cancer outcomes trajectory. Therefore, we propose to have a new composite endpoint which encompass the survival (i.e., death), tumor relapse (i.e., LF, RF, and DM), and laryngo-esophageal dysfunction (i.e., speech and swallowing).

In this study, we aimed to retrospectively evaluate the oncologic and functional outcomes of stage III-IVb LSCC patients treated at our institution with functional-preservation strategy with a specific focus on laryngo-esophageal dysfunction disease-free survival (LEDDFS).

2 | METHODS

2.1 | Study population

After institutional review board (IRB) approval (IRB No. 21 KHCC 191), we identified all laryngeal cancer patients with newly diagnosed, previously untreated, pathologically confirmed non-metastatic stage III-VIb SCC of the larynx according to the seventh edition of the TNM staging system jointly used by the American Joint Committee on Cancer and Union of the International Cancer Control (AJCC/UICC).[18] Patients treated with curative-intent primary RT at our institution between 2007 and 2018 were included in this retrospective analysis. Patients younger than 18 years, those with histopathology other than squamous cell carcinoma (SCC), or who received previous RT to the head and neck region, or had any second primary cancer, stage I and II laryngeal SCC, or received RT dose below 50 Gy and or large T3/T4a who underwent upfront total laryngectomy were excluded from this analysis. The patient's demographics and clinical information including outcomes were retrospectively collected from patient's medical records.

2.2 | Diagnostic approach

Staging work up and pre-treatment evaluation consisted of history and comprehensive physical examination including assessment with fiberoptic endoscopy, head and neck MRI or CT scan and PET/CT or CT scan of the chest, abdomen, and pelvis. After completion of staging work up, all patients were discussed and managed by a multidisciplinary head and neck team, with pre-RT evaluation by dedicated teams of dental oncologist, nutritionists, and speech/language pathologists.

2.3 | Treatment approach

All patients, who were selected for functional preservation strategy, were routinely offered upfront CCRT; except for: (1) those with cN2-3, cT4, or large volume cT3, when IC followed by CRT was an alternative option, and (2) those who were unfit or declined chemotherapy (received accelerated RT or hyperfractionated RT according to patient's PS and radiation oncology preference).

The dose and fractionation schedules of the selected RT regimens were described in Table S1. RT was delivered using 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) techniques. For patients who received upfront CCRT, the concurrent radiosensitizing agent consisted of high-dose cisplatin (100 mg/m^2 given on days 1, 22, and 43) or low-dose cisplatin (40 mg/m^2 weekly during RT). In patients managed with IC followed by CCRT, they received the induction DCF regimen (docetaxel [75 mg/m^2] and cisplatin [100 mg/m^2] on day 1, and 5-fluorouracil [1000 mg/m^2] on days 1–5; every 3 weeks for three cycles), followed by concurrent weekly carboplatin (area under the curve [AUC] of 1.5) during RT. For patients with contraindication to cisplatin, carboplatin replaced cisplatin whether patients were planned to be managed with upfront CCRT or IC followed by CCRT. Salvage surgery was performed for medically fit patients with biopsy-proven local and/or regional recurrence with no evidence of DM.

2.4 | Post-treatment evaluation and follow-up

Patients were reviewed in the multidisciplinary head and neck clinic 2 weeks after the end of RT, then every 3 months for the first 2 years, every 4 months in the third year, every 6 months in the fourth and fifth year, and annually thereafter until death. Post-treatment imaging to evaluate response to therapy-included head and neck MRI or CT scan and PET/CT, which was performed 10–12 weeks after the end of RT, then as clinically indicated. Severe late RT-related side effects were defined as late RTOG grade ≥3 toxicity starting >6 months after the end of RT.

2.5 | Statistical methods

The primary endpoint was 3-year LEDDFS, and secondary endpoints were 3-year LF, RF, DM, OS, disease-free survival (DFS), and acute and late toxicities. LEDDFS, OS, and DFS were analyzed using the Kaplan–Meier method and compared using the log-rank test. LF, RF, and DM rates were estimated using the cumulative incidence method using Gray's test, with death as a competing risk. Events for LEDDFS included death, tumor relapse (i.e., LF, RF, and DM), and late laryngo-esophageal dysfunction (defined by feeding tube dependence, tracheostomy, or aspiration pneumonia >6 months post-RT). Acute and late toxicity rates were estimated by cumulative incidence function. Multivariable analysis (MVA) using Cox proportional hazards regression was used to identify predictors of LEDDFS, OS, and DFS. All reported p-values were two-sided, with a statistical significance level of $p \leq .05$. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC), and the figures were performed using GraphPad PRISM 7.

3 | RESULTS

3.1 | Patient, tumor, and treatment characteristics

Patients, tumor, and treatment characteristics were summarized in Table 1. A total of 213 LSCC patients were identified, of whom 154 patients (72%) were treated with CCRT; 34 patients (16%) received IC followed by CCRT and 25 patients (12%) were not fit for chemotherapy and received accelerated RT. Among the entire groups, the majority of patients (62%) were treated with IMRT. There were significant differences between treatment groups in terms of pre-treatment age ($p \leq .001$), Eastern Cooperative Oncology Group (ECOG) performance status (PS) ($p \leq .001$), smoking history ($p < .048$), primary tumor subsite ($p < .04$), cT-category ($p < .01$), and cN-category ($p < .01$) as shown in Table 1.

3.2 | Primary outcome: LEDDFS

For the entire cohort, the 3-year LEDDFS was 50% (95% CI, 42%–57%) (Figure 1). There were no statistically significant differences in 3-year LEDDFS rates between the three treatment groups (CCRT group; 52% [95% CI, 43%–61%]) versus (IC group; 43% [95% CI, 26%–62%]); $p = .31$ versus (accelerated RT group; 41% [95% CI, 21%–62%]). By delivered RT technique, there were no statistically significant differences in 3-year LEDDFS rates between RT techniques (IMRT vs. 3DCRT); (IMRT; 45% [95% CI, 35%–54%]) versus (3DCRT; 58% [95% CI, 45%–70%]), $p = .14$.

3.3 | Tumor control outcomes

For the entire cohort, the 3-year LF, RF, and DM cumulative incidence rates were 9% (95% CI, 5%–14%), 5% (95% CI, 2.17%–8.71%), and 7% (95% CI, 3.50%–12%), respectively as shown in Figure 2.

Fifteen patients developed LF at the median time of 9 months post-RT (range: 3–70). Of whom, six patients had persistent local disease following treatment, seven patients had no DM at the time of LF, and were salvaged with total laryngectomy. None of the salvaged patients recurred on the last follow up.

Seven patients developed RF at the median time of 9 months post-RT (range: 2–36). Of whom, five patients had residual neck nodes following treatment, four patients had no DM at the time of RF, and were salvaged with neck dissection. None of the salvaged patients recurred on the last follow up.

Fourteen patients developed DM at the median time of 28 months post-RT (range: 4–54). Of whom, four patients had DM with LRF, four patients had DM with local-only failure and one patient had DM with regional-only failure, while five patients developed distant-only failure. The most common site of DM was lung ($n = 11$, 79%). All metastatic patients were treated with palliative chemotherapy. The median time from DM to death was 8 months (range: 0.6–35).

3.4 | Survival outcomes

For the entire cohort, the 3-year OS and DFS were 81% (95% CI, 75–87) and 74% (95% CI, 67–80), respectively (Figure 1). There was statistically significant difference in 3-year OS rates between treatment groups; (CCRT group; 86% [95% CI, 79%–91%]) versus (IC group; 66% [95% CI, 45%–84%]) versus (accelerated RT group; 75% [95% CI, 54%–91%]), $p = .03$ and a trend toward superior 3-year DFS rate in the CCRT group; (CCRT group; 78% [95% CI, 70%–85%]) versus (IC group; 58% [95% CI, 39%–76%]) versus (accelerated RT group; 66% [95% CI, 45%–85%], $p = .06$).

3.5 | Functional and toxicity outcomes

For the whole cohort, late (>6 months after RT) laryngo-esophageal dysfunction (LED) was reported in 68 patients (32%), including: tracheostomy ($n = 25$, 12%), feeding tube dependence ($n = 15$, 7%), and aspiration pneumonia ($n = 4$, 2%) as shown in Table 1. By RT technique (IMRT vs. 3DCRT), LED was reported in ($n = 46$, 35%) versus ($n = 22$, 27%) patients, $p = .6$. In all groups, there were no grade 4 or 5 acute and late RTOG toxicity. Grade 3 acute and late skin toxicity

TABLE 1 Patients, tumor, and treatment characteristics

Variable		Whole cohort ($N = 213$)	Sub-groups			p value
			CRT $n = 154$ (72%)	Accelerated radiotherapy $n = 25$ (12%)	Induction chemotherapy $n = 34$, (16%)	
Follow up, median (range), months		37.6 (1–172)	37 (1.4–172)	44 (3.3–140)	25 (1.0–102)	.487
Age, median (range), years		59 (37–100)	57 (37–88)	72 (42–100)	57.5 (46–75)	**.001**
Gender	Male	191	136 (88%)	24 (96%)	31 (91%)	.59
	Female	22	18 (12%)	1 (4%)	3 (9%)	
ECOG performance status	0–1	195	152 (100%)	9 (39%)	34 (100%)	**<.001**
	2	14	0	14 (61%)	0	
	Not reported	4	2 (0%)	2 (0%)	0	
Smoking	Yes	177	131 (87%)	16 (67%)	30 (88%)	**.048**
	No	32	20 (13%)	8 (33%)	4 (12%)	
	Not reported	4	3 (0%)	1 (0%)	0	
Drinking	Yes	4	3 (2%)	1(4.2%)	0	.48
	No	205	148 (98%)	23 (96%)	34 (100%)	
	Not reported	4	3 (0%)	1 (0%)	0	
Disease subsite	Supraglottis	65	48 (31%)	6 (24%)	11 (32%)	**.04**
	Glottis	44	34 (22%)	7 (28%)	3 (9%)	
	Subglottis	2	0	2 (85)	0	
	Overlapping	102	72 (47%)	10 (40%)	20 (59%)	
T-category	T1	4	3 (2%)	0	1 (3%)	**<.01**
	T2	8	6 (4%)	0	2 (6%)	
	T3	159	125 (81%)	14(56%)	20 (59%)	
	T4	42	20 (13%)	11(44%)	11 (32%)	
N-category	N0	110	84 (55%)	16(64%)	10 (29%)	**<.01**
	N1	32	22 (14%)	1(4%)	9 (27%)	
	N2	65	46 (30%)	8(32%)	11 (32%)	
	N3	6	2 (1%)	0	4 (12%)	
Radiotherapy technique	3DCRT	81	57 (37%)	11(44%)	13 (38%)	.80
	IMRT	132	97 (63%)	14 (56%)	21 (62%)	
Laryngo-esophageal dysfunction type ($n = 68$)	Aspiration pneumonia	4 (6%)	4 (8%)	0	0	.34
	Feeding tube dependence	15 (22%)	12 (24%)	2 (22%)	1 (10%)	
	Feeding tube dependence/ aspiration pneumonia	1 (1%)	0	0	1 (10%)	
	Tracheostomy	25 (37%)	16 (33%)	5 (56%)	4 (40%)	
	Tracheostomy/ aspiration pneumonia	2 (3%)	1 (2%)	1 (11%)	0	
	Tracheostomy/ feeding tube dependence	21(31%)	16 (33%)	1 (11%)	4 (40%)	

Abbreviation: CRT, concurrent chemoradiation.

were found in 6% and 15%, respectively. Grade 2 acute and late xerostomia were reported in 86% and 85%, respectively. Grade 2 acute mucositis was found in 30% of patients. The most common grade ≥3 acute and late RTOG toxicity were esophageal toxicity: 16.7% and 29.6%, respectively.

For IMRT versus 3DCRT, acute and late RTOG grade 2 xerostomia were found in ($n = 75$, 57% and $n = 74$, 56%) versus ($n = 54$, 67% and $n = 51$, 63%) and grade 2–3 esophageal and laryngeal toxicities were found in ($n = 103$, 78% and $n = 62$, 47%) versus ($n = 62$, 77% vs. $n = 37$, 46%), respectively.

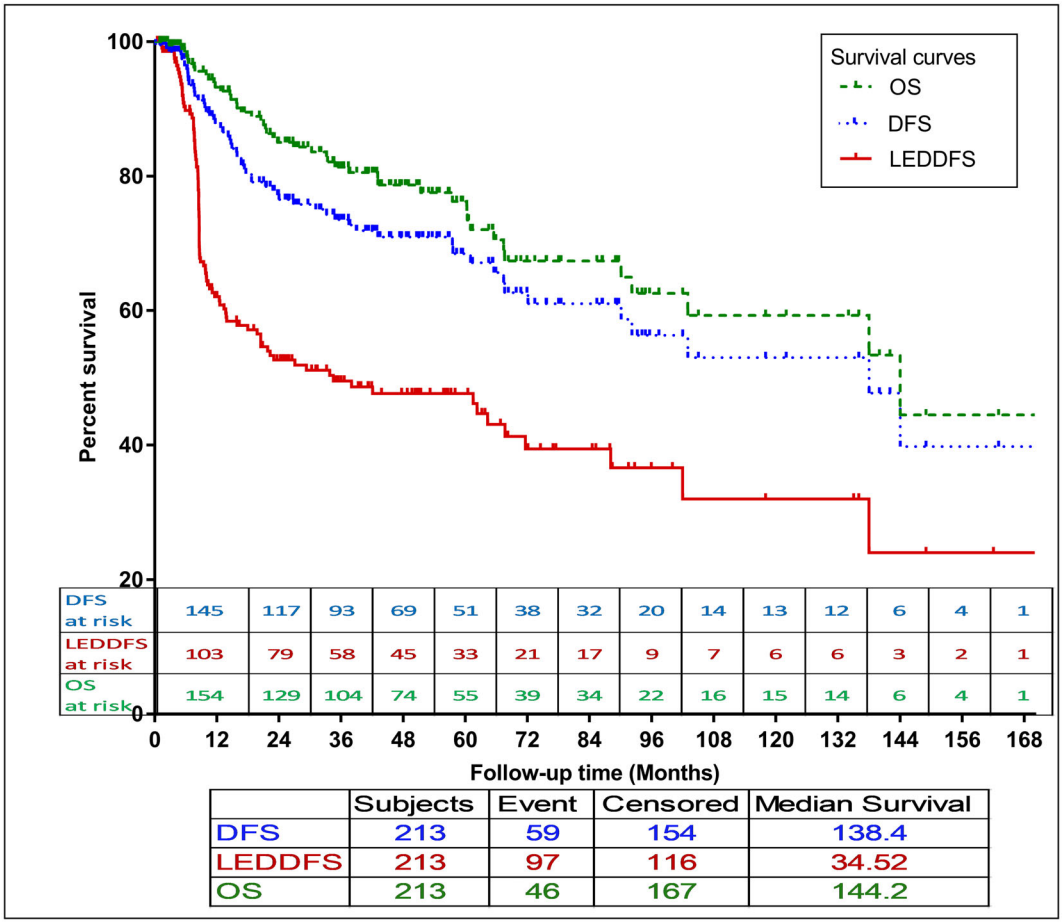

FIGURE 1 Kaplan–Meier curve for laryngo-esophageal dysfunction disease free survival (LEDDFS), overall and disease free survival in the entire study population

3.6 | Outcome predictors

On MVA, cT4-category was associated with inferior LEDDFS (HR: 0.47, [95% CI: 0.29–0.74], $p < .01$), OS (HR: 0.43, [95% CI: 0.21–0.86], $p < .02$), and DFS (HR: 0.47, [95% CI: 0.25–0.87], $p < .01$), see Table 2. In addition, age < 60 years (HR: 1.79, [95% CI: 1.04–3.09], $p < .03$) was a predictor for superior DFS.

4 | DISCUSSION

This study identified the 3-year oncologic and functional outcomes in patients with stage III-IVb LSCC who were treated with CCRT, IC followed CCRT or accelerated RT at our institution. To our knowledge, this is the first and largest retrospective report from the Middle East region focused on LEDDFS in locally and or locoregionally advanced LSCC. This study demonstrated a 3-year LEDDFS rate of 50%, with no statistically significant differences in 3-year LEDDFS rates between treatment groups. Furthermore, cT4-category was a poor predictor for LEDDFS, DFS, and OS.

The current study focused on LEDDFS as the primary endpoint, while several retrospective studies evaluated the LEDFS as the main outcome of interest (which did not incorporate the RF and DM as part of this composite endpoint). For example, Caudell et al. reported 3-year LEDFS rate of 28.9% in 105 patients with stage III and IVb LSCC and found no statistically significant differences in LEDFS among different T-categories based on their study population.[19] Furthermore, LEDFS was also evaluated in 104 patients with T3 LSCC, treated with a laryngeal-preservation protocol with IC, and the 2-year and 5-year LEDFS rates were 44.3% and 28.2%, respectively. LEDFS was not associated with initial hemilaryngeal fixation or subglottis extension ($p = .5772$ and $p = .0623$, respectively).[20] Unfortunately, it is challenging to compare the primary end point of our results with these studies due to different population among these studies, and the inclusion of RF and DM in our composite endpoint (i.e., LEDDFS vs. LEDFS). However, we believe that LEDDFS is the accurate composite endpoint because it incorporates RF and DM, both of which are included in the DFS definition.

The 3-year OS, DFS, LF, and RF and DM rates among the entire study cohort were 81%, 74%, 9%, 5%, and 7%, respectively, which are relatively favorable compared to other published studies,[19,21–24] that is, Corry et al. has reported 3-year OS, failure-free survival (FFS), regional control (RC), and local control (LC) rates of 67%, 66.3%, 96%, and 83%, respectively on 60 patients with advanced LSCC treated

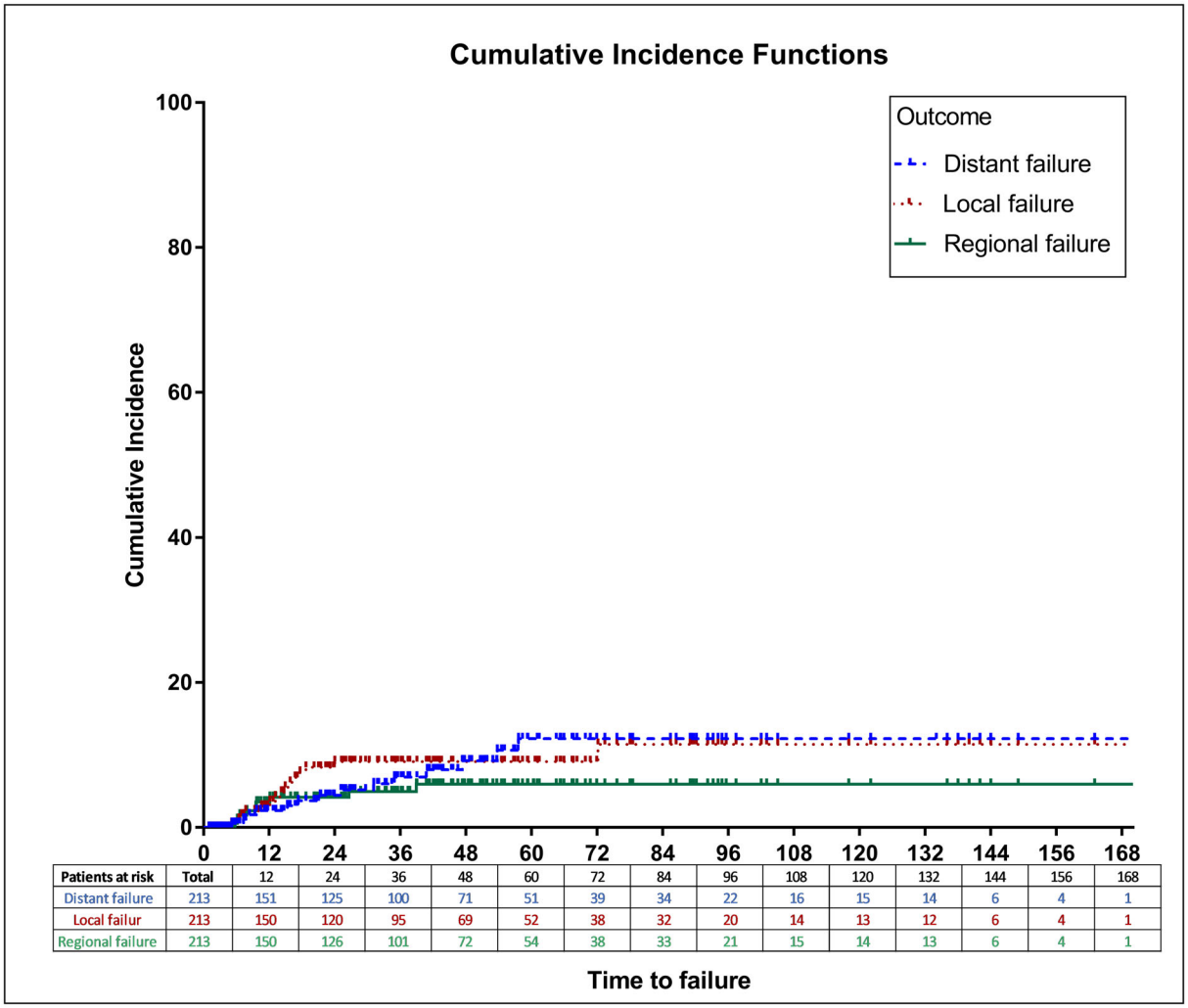

FIGURE 2 Cumulative incidence method for local, regional, and distant failures in the entire study population

with RT based organ preservation approaches,[24] however, such comparison is fairly difficult given the heterogeneity of tumor, treatment characteristics, length of follow up and primary and secondary endpoints studied among different studies. In addition, we found that there was statistically significant difference in 3-year OS rates between treatment groups favoring CCRT; (CCRT group; 86%) versus (induction chemotherapy group; 66%), and (accelerated RT group; 75%), $p = .03$. However, the results from the landmark laryngeal preservation trial RTOG 91-11 reported no statistically significant differences in OS among the different treatment groups.[9]

In the T4 category, the main point of discussion between oncologists and laryngeal patients is clinical outcomes and quality of life with the organ preservation approach relative to total laryngectomy.[25] Grover et al. studied 616 T4a LSCC patients. One-thirds underwent total laryngectomy followed by adjuvant treatment. The median OS for total laryngectomy followed by adjuvant treatment versus CCRT was 61% versus 39% months ($p = .001$).[26] Not all of the retrospective studies found that total laryngectomy followed by adjuvant treatment was superior to primary CCRT in terms of OS.[27,28] Furthermore, the results from previous studies showed that cT4-category was a poor predictor for OS and DFS when advanced LSCC treated with RT based organ preservation approaches.[29–31] Our study reported the same finding, and also found that cT4-category predicted for poor LEDDFS, which reflects the reality that the standard treatment approach for cT4 disease should be total laryngectomy.[29] Total laryngectomy was more frequently used to treat T4-category LSCC patients in high-volume centers than in low-volume centers (46.1% vs. 31.5%; $p = .001$).[32,33]

With a median follow-up of 37 months, only-half of our patients with locoregionally advanced LSCC had favorable oncologic and functional outcomes. According to Timme et al., who included 102 patients treated with RT (82.4% T3) and 20 patients' treated with CCRT (60.0% T3), LEDFS at 2 years for T3 tumors treated with RT or CCRT was 40%, the rates of tracheostomy feeding tube dependent were 25% and 12%, respectively.[34] Vengalil et al. has reported on 65 LSCC patients and found a 2-year tracheostomy-dependency rate of 55% following RT or CCRT.[28] Among our study population, the rate of late tracheostomy was 12% (comparable to what was reported in

TABLE 2 Univariable and multivariable analysis of prognostic factors for laryngeal dysfunction disease free survival, overall survival, and disease free survival

Variable	Laryngo-esophageal dysfunction disease free survival				Overall survival				Disease free survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age > 59 versus ≤ 59	0.88 (0.59–1.32)	.53			1.79 (0.99–3.21)	.051			1.73 (1.03–2.89)	.04	1.79 (1.04–3.09)	**.04**
Female versus male	0.76 (0.38–1.52)	.43			0.45 (0.14–1.48)	.19			0.66 (0.26–1.68)	.39		
PS 0 versus PS 1–2	1.07 (0.68–1.70)	.76			0.68 (0.37–1.27)	.23			0.67 (0.39–1.17)	.16		
Smoking, yes versus no	1.22 (0.68–2.2)	.51			1.69 (0.66–4.33)	.28			1.51 (0.68–3.35)	.31		
Drinking, yes versus no	1.21 (0.3–4.92)	.79			1.19 (0.16–8.66)	.86			2.33 (0.57–9.59)	.24		
T1–T3 versus T4	0.452 (0.287–0.713)	<.01	0.46 (0.29–0.74)	**<.01**	0.34 (0.18–0.65)	<.01	0.43 (0.21–0.86)	**.02**	0.35 (0.2–0.62)	**<.01**	0.47 (0.25–0.87)	**.02**
N0 versus N1–N3	0.59 (0.39–0.88)	<.01			0.83 (0.46–1.49)	.53			0.62 (0.37–1.04)	.07		
CCRT versus accelerated RT	0.75 (0.41–1.37)	.35			0.54 (0.23–1.25)	.15			0.55 (0.26–1.15)	.11		
Induction chemo versus accelerated RT	1.08 (0.53–2.24)	.83			1.27 (0.5–3.24)	.62			1.06 (0.45–2.48)	.9		
Glottis versus overlapping	0.48 (0.26–0.89)	.02			0.40 (0.15–1.05)	.06			0.52 (0.24–1.14)	.1		
Subglottis/supraglottis versus overlapping	1 (0.65–1.57)	.98			0.74 (0.39–1.43)	.37			0.82 (0.46–1.46)	.49		

Note: Significant *p*-values in bold.

Abbreviations: CI, confidence interval; HR, hazard ratio; PS, performance status.

literature between 8.2% and 55%[28,35–37]), and the late aspiration pneumonia rate was 2% (similar to what was reported by Anschuetz et al. 1.8%).[4] Moreover, late feeding tube dependence was observed in 7% of patients which is comparable to a systematic review by Wopken et al. (2-year feeding tube dependence varied from 3.7% to 12%).[34,38] In our cohort, the use of IMRT versus 3DCRT did not improve the rates of LED, acute and late RTOG grade 2 xerostomia and grade 2–3 esophageal and pharyngeal toxicities similar to what was reported by RTOG 0522 which demonstrated no difference in grade 2–3 laryngitis (26.7 vs. 18.4%, $p = .05$), grade 2 xerostomia (38.2 vs. 34.2%, $p = .40$) and feeding tube use (22.8%) versus (21.9%) in laryngeal cancer patients.[39]

Our study is subject to selection bias due to its retrospective design. The assessment of voice quality was not feasible from medical records. We reported LEDDFS as a composite endpoint that can be used to evaluate future functional preservation clinical trials. This study contributes toward predicting patients with poor LEDDFS who may benefit from organ preserving treatment or experimental approaches.

5 | CONCLUSIONS

Primary RT resulted in favorable oncologic and functional outcome in only half of the advanced stage laryngeal cancer patients. Future clinical trials are required to investigate further treatment particularly in T4-primary tumors aiming to improve the oncologic and maintain functional outcomes with utilization of LEDDFS as the primary endpoint.

CONFLICTS OF INTEREST

Dr Ali Hosni declare non-related, non-financial: disease site chair of Liver Tumor Site Group of ELEKTA MRL-consortium. All other co-authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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