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HEAD & NECK

Organ-preservation (chemo)radiotherapy for T4 laryngeal and hypopharyngeal cancer: is the effort worth?

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Abstract

Purpose We aimed to analyze the oncological and functional outcomes of chemoradiation for T4 laryngeal and hypopharyngeal cancer.

Methods Patients treated between 2008 and 2015 with chemoradiation ($n=39$) were retrospectively analyzed for oncological and functional (laryngo-esophageal dysfunction-free survival, LED-FS) outcomes and compared with 32 consecutive patients treated primarily with total laryngectomy (TL). LED was scored as event in case of local failure, TL for any reason, persistent tracheotomy and/or feeding tube dependency 2 years after chemoradiation.

Results The 5-year local control (LC) rates in the chemoradiation and TL groups were 64 and 87%, respectively ($p=0.030$). The disease-free survival was 54 and 59% ($p=0.810$), and overall survival (OS) was 46 and 47% ($p=1.00$). In the chemoradiation group, the 5-year cumulative incidence of LED-FS was 46%, but was significantly worse in patients with poor pre-treatment laryngeal function, compared to those without (20% and 74%, respectively, $p=0.001$). Furthermore, patients with LED have significantly worse OS compared to those without (32% and 65%, respectively, $p=0.041$). Multivariate analysis showed that primary treatment type is significantly predictive for LC, while tumor site and extra-capsular extension were predictive for OS. Poor pre-treatment laryngeal function is the only significant predictive factor for LED.

Conclusions TL resulted in significantly better LC, as compared to chemoradiation in T4 laryngeal and hypopharyngeal cancer patients and the LED-FS is worse in patients with poor pre-treatment laryngeal function. These patients might benefit more from primary treatment with TL followed by radiotherapy. These issues should be taken into consideration, as patients are counseled about different primary treatment options.

Keywords Laryngeal cancer · Hypopharyngeal cancer · Organ preservation · Chemoradiation · Total laryngectomy

Introduction

Chemoradiation (CRT) has been adopted as organ-preservation treatment modality for locally advanced (T3–4 tumor) laryngeal cancer (LC) in properly selected patients [1]. In the light of these results, CRT has also been studied as first line treatment for the smaller subgroup of locally advanced hypopharyngeal cancer (HPC) [2, 3]. Until recently, there was no clear consensus about the optimal treatment modality for T4 tumors from these subsites, because the randomized studies considered as landmark trials reporting on outcome of these patients have included only small number of patients with T4 disease [4–7]. Although the National Comprehensive Cancer Network (NCCN) guidelines currently recommended concurrent CRT only for selected T4a LC and HPC patients who decline surgery, the majority of

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these patients are still currently treated with concurrent CRT despite the lower survival rates, compared to those treated with total laryngectomy (TL) and postoperative radiotherapy (PORT) (median survival of 39 and 61 months, respectively, $p < 0.001$) [8]. In that study, 64% of patients diagnosed with a T4 tumor identified at the National Cancer Database still underwent larynx-preservation CRT.

The major concern when these patients are treated with CRT is the higher incidence of local failure (LF) which would not be adequately and timely salvaged by TL with subsequent detrimental effect on survival and quality of life (QoL) of these patients. However, a subgroup of these patients might still benefit from CRT. The dilemma is the paucity of information about which subgroup of T4 patients actually might benefit from primary CRT. The guideline update of the American Society of Clinical Oncology Clinical Practice recommended TL for patients with large volume T4 tumor and/or poor pre-treatment laryngeal function, since TL has shown to results in better survival and QoL, compared to CRT or radiotherapy alone [9]. However, the definition of poor pre-treatment laryngeal function is not uniform.

In the current study, we retrospectively analyzed the oncological and functional outcomes of consecutive patients with T4 LC and HPC treated at our institution with CRT. We also aimed to identify which subgroup of patients might still benefit from organ-preservation CRT.

Materials and methods

Ethical considerations

This article does not contain any experimental study with human participants performed by any of the authors. No identifying information is included in this article The local institutional review board waived informed consent for this retrospective analysis of clinical data.

Study population

Between July 2008 and January 2016, 39 consecutive patients diagnosed with a T4 laryngeal or hypopharyngeal squamous cell carcinoma were treated with curative intent in our institution with organ-preservation (chemo)radiation (group A). To compare the outcomes of these patients with those who were primarily treated with TL followed by PORT (group B), we identified all consecutive patients ($n = 32$) treated in our institution at the same time period. Data from these patients was retrospectively collected for the current study.

Diagnostic workup consisted of complete history and physical examination, including examination under general anesthesia with histologic biopsy of the tumor. Ultrasound with fine needle aspiration cytology (FNAC) when indicated, head and neck CT scan and ^{18}F-FDG-PET were acquired in all patients with T4 tumors. All patients were discussed at the weekly multidisciplinary head and neck tumor board for primary treatment recommendations. Primary CRT was advocated for low-volume disease and in patients refused primary TL. Patients were subsequently evaluated by the medical oncologist whether they are fit enough for cisplatin-based CRT. Primary TL followed by radiotherapy was advocated for patients with bulky tumors, overt extra-laryngeal extension, and/or cartilage destruction.

Primary (chemo)radiotherapy or postoperative (chemo)radiotherapy

In group A, the radiation dose to the primary tumor and involved node(s) was 70 Gy, and in group B, this was 56–66 Gy. In group B, patients with high-risk disease (closed margins < 1 mm and/or extra-capsular extension) received 66 Gy and when fit also concomitant cisplatin and patients with intermediate-risk disease (safe margins 1–5 mm, perineural invasion, N2b disease) received 56 Gy postoperatively. All patients were treated with intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). The radiation was given in five fractions a week. Chemotherapy was given as 3-weekly concomitant intravenous high-dose cisplatin (100 mg/m^2 on days 1, 22, and 43 of RT). Low-dose daily cisplatin was given in a daily dose of 6 mg/m^2 for 5 weeks (week 1–5 of radiotherapy) (cumulative dose of 150 mg/m^2) to elderly or frail patients.

Follow-up

During treatment patients were seen twice weekly at the outpatients clinic to monitor the acute toxicities. After completion of treatment, patients were seen every 2 weeks until the acute toxicity had subsided. In group A, the response evaluation was done by means of CT scan and ultrasound with FNAC when indicated. In case of any suspicion of residual disease, examination under anesthesia was performed. Thereafter, patients were followed up 3 monthly for the first year, 4 monthly for the second year, and 6 monthly thereafter.

End points

The primary end point of the current study is to compare the oncological outcomes of both groups with regard to local control, loco-regional control (LRC), disease-free survival (DFS) (local, regional, or distant metastatic disease were recorded as events, censoring for death), and overall survival (OS). In group A, beside these oncological outcomes, a composite functional endpoint was calculated

for these patients: laryngo-esophageal dysfunction (LED)-free survival (LED-FS) (LF, TL for any reason, persistent tracheotomy and/or feeding tube dependency 2 years after CRT were recorded as an event, death censored). The independent variables used were age, smoking status, tumor sites, treatment group, nodal stage, the presence of extracapsular extension, tumor volume, the use of systemic therapy, pre-treatment tracheotomy, radiological and clinical sings of poor pre-treatment laryngeal function. Extralaryngeal tumor extension was defined as a radiological sign of poor pre-treatment laryngeal function. Stridor or airway obstruction needing tracheotomy, repeated aspiration pneumonia or grade 2–3 dysphagia at baseline were defined as clinical signs of poor pre-treatment laryngeal function.

Statistical analysis

Variables are presented as percentage, mean (± SD) or median (+ interquartile range) in case of a skewed distribution. Differences in baseline characteristics between group A and Group B were tested using Student's *t* tests (continuous variables) and Chi-square tests (categorical variables).

The follow-up duration was calculated as the time from start of radiotherapy in group A and date of TL in group B until date of death or last follow-up for overall survival. DFS was calculated until the date of first progression (local, regional, and distant) or last date of follow-up or death. Local control was calculated until the date of first local progression or last date of follow-up or death. LRC was calculated until the date of first local or regional progression or last date of follow-up or death. Kaplan–Meier survival curves were plotted for local control, LRC, DFS, and OS. Statistical significance between the two groups was calculated with Log-Rank tests. To investigate factors influencing local control and OS, cox proportional hazard analyses were performed. First, univariate analyses were constructed, and second, a multivariate model was constructed using a backward selection procedure. In this method, all variables with a p value < 0.1 in univariate analyses are included. With each consequent step, the least significant variable is excluded from the model until all remaining variables are statistically significant. Proportional hazard assumptions for every model were tested by interpretation of the survival plots. Data are presented as Hazard Ratios (HR) with 95% confidence intervals (CI), which can be interpreted as relative risks. Sensitivity analyses were performed to assess factors associated with LED in group A, using univariate and multivariate logistic regression analyses. p values less than 0.05 were considered statistically significant. All analyses were performed in SPSS for Windows (v22.0.0.0, IBM Corporation).

Results

Patient's demographics are shown in Table 1. Patients treated primarily with (chemo)radiation (group A) had significantly more HPC than LC, low-volume tumors, node-positive disease, less signs of poor pre-treatment laryngeal function and less frequently pre-treatment tracheotomy, compared to patients treated primarily with TL followed by PORT.

In group A, all patients received 70 Gy of radiotherapy. Eleven patients (28%) did not receive chemotherapy because of age > 70 years ($n = 4$), severe comorbidities ($n = 6$), or patient's refusal ($n = 1$).

In group B, the dose of postoperative radiotherapy ranged between 56 and 66 Gy (median 66 Gy). Three patients refused the PORT, nine patients received 56 Gy because of intermediate-risk disease, and 20 patients received 66 Gy because of high-risk disease. Four patients (13%) received postoperative CRT.

After a median follow-up of 67 months (range 38–86) for the whole group, the 2-year cumulative incidence of local control, LRC, DFS, and OS were 75%, 65%, 58%, and 54%, respectively. The 5-year figures for local control, LRC, DFS, and OS were 75%, 65%, 56%, and 46%, respectively.

When the outcome was analyzed by treatment group, the 5-year cumulative incidence of local control in groups A and B was 64 and 87%, respectively ($p = 0.030$). For LRC, this was 62 and 69% ($p = 0.474$), for DFS 54 and 59% ($p = 0.810$) and for OS 46 and 47%, respectively ($p = 0.482$) (Fig. 1). When the outcome was analyzed by tumor site, the 5-year cumulative incidence of local control for patients with LC and HPC was 84% and 65%, respectively ($p = 0.046$). For LRC, this was 68 and 58% ($p = 0.609$), for DFS 62 and 40% ($p = 0.302$), and for OS 60 and 32%, respectively ($p = 0.022$) (Fig. 2). In group A, 11 patients (28%) received only radiotherapy without systemic therapy. The 5-year cumulative incidence of local control in those patients, compared to those who received systemic therapy, was 55% and 68%, respectively ($p = 0.478$). The figures for LRC were 55 and 65% ($p = 0.718$), for DFS were 46 and 57% ($p = 0.723$), and for OS were 55 and 43% ($p = 0.723$). With regard to the functional outcome of patients treated in group A, LED was scored as event in 22 patients (56% of the whole group); eight patients had inoperable LF, eight patients underwent TL (six because of LF and two because of functional failure) and six patients had persistent tracheotomy and/or feeding tube 2 years after CRT. The 5-year cumulative incidence of LED-FS was 46%, respectively. The 5-year cumulative incidence of LED-FS in patients with and without poor pre-treatment laryngeal function

Table 1 Patients' characteristics

	Group A; (C)RT ($n=39$)	Group B; TL ($n=32$)	p value
Age in years, mean (SD)[a]	62 (9)	65 (10)	0.13
Male (%)[b]	35 (90)	27 (84)	0.72
Follow-up in months, median (range)	71 (47–80)	67 (37–88)	0.94
Smoking status (%)			
Still smoking	29 (74)	21 (66)	0.45
Stopped > 2 years ago	10 (26)	11 (34)	
Tumor site[b] (%)			
Larynx	16 (41)	21 (66)	0.04
Hypopharynx	23 (59)	11 (34)	
Tumor volume (cc)			
Median	35.1	52.7	0.02
Range	23.3–61.2	40.7–78.9	
N-classification (%)			
N0	11 (28)	12 (38)	0.03
N1	1 (3)	6 (19)	
N2	22 (56)	14 (53)	
N3	5 (13)	0 (0)	
Extra-capsular extension (%)			
Yes	7 (18)	11 (34)	0.11
No	32 (82)	21 (66)	
Radiological sign of PPLF[b] (%)			
Yes	18 (46)	28 (87)	< 0.001
No	21 (54)	4 (13)	
Clinical signs of PPLF[b] (%)			
Yes	20 (51)	25 (78)	0.02
No	19 (49)	7 (22)	
Tracheostomy before primary treatment (%)			
Yes	6 (15)	11 (34)	0.06
No	33 (85)	21 (66)	
Systemic therapy (%)			
Yes	28 (72)	4 (13)	< 0.001
No	11 (28)	28 (87)	

(C)RT (chemo)radiation, *TL* total laryngectomy, *PPLF* poor pre-treatment laryngeal function

[a]Statistically significant differences were tested using Student's t tests for continuous variables

[b]Chi-square tests for categorical variables

was 20% and 74%, respectively ($p=0.001$) (Fig. 3). The 5-year cumulative incidence of LED-FS in patients treated with radiotherapy alone, compared to those who received systemic therapy, was 36 and 50% ($p=0.497$).

With regard to the impact of functional problems on survival, the 5-year cumulative incidence of OS in patients with LED vs those without LED was 32% and 65%, respectively ($p=0.041$). The figures for patients with and without tracheotomy were 35% and 50%, respectively ($p=0.667$).

Multivariate analysis showed that primary treatment type was significantly predictive for local control [primary TL significantly better local control, compared to primary CRT, while tumor site (HPC worse compared to LC) and the presence of extra-capsular extension were significantly predictive for poor OS (Table 2)]. In group A, the presence of clinical signs of poor pre-treatment laryngeal function is the only significant predictive factor for LED in the multivariate analysis (Table 3).

Discussion

In patients with laryngeal and hypopharyngeal cancer, preservation of a functional larynx and normal swallowing function after an organ-preservation approach is of utmost importance, since speech and swallowing functions have a

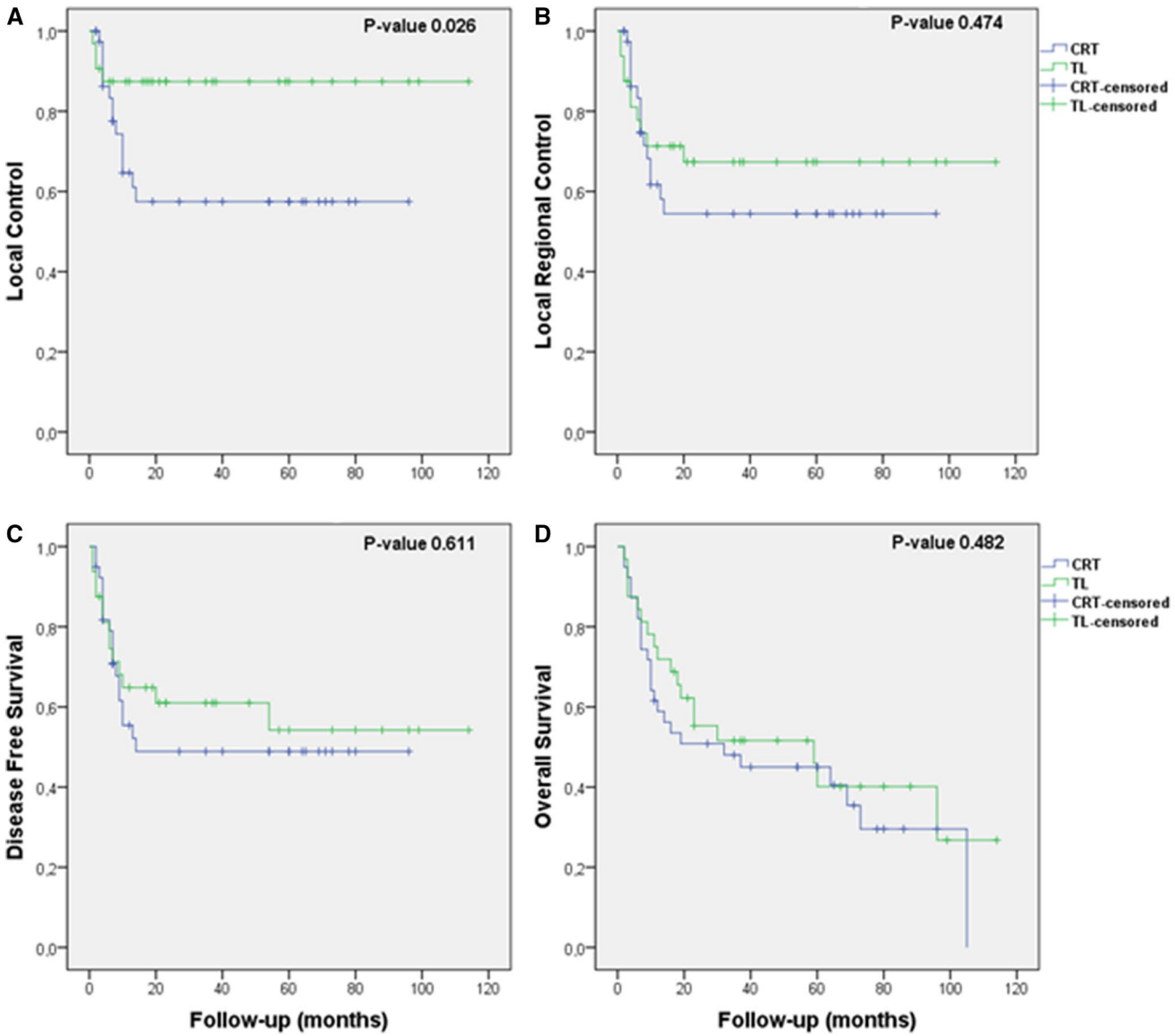

Fig. 1 Kaplan–Meier curves for local control (**a**), loco-regional control (**b**), disease-free survival (**c**), and overall survival (**d**), by treatment group. *CRT* Chemoradiation, *TL* total laryngectomy

significant impact on the patient's QoL. Although TL and PORT should be the standard treatment for T4 tumors, a considerable proportion of these patients are still treated with CRT [8]. However, there are growing concerns that the currently used non-surgical management for locally advanced disease might end up with functional failure because of the need of TL due to laryngeal and/or swallowing dysfunction, long-term tracheotomy, and/or gastrostomy tube dependency [10–18]. Furthermore, the long-term results of the Radiation Therapy Oncology Group (RTOG) 91-11 [3] trial showed an increased number of non-laryngeal cancer-related deaths in the CRT arm, which could be related to the long-term toxicities of this approach. Nevertheless, a subset of these patients might still benefit from organ-preservation CRT in terms of oncological and functional outcomes. The pivotal question is which subgroup of these patients would benefit more from primary CRT. In the current study, primary TL resulted in significantly better local control compared to CRT, however, without significant improvement in OS. The multivariate analysis showed that primary treatment with TL was the only significant predictor for better local control, while extra-capsular extension and hypopharyngeal compared to laryngeal cancer were predictive for poor OS.

The data on the impact of pre-treatment tracheotomy on oncological and functional outcomes are not very clear, as some reported an adverse prognostic impact of tracheotomy on survival [12, 18, 19], while other authors [20] failed to show any correlation. Furthermore, Byrd et al. [12] have

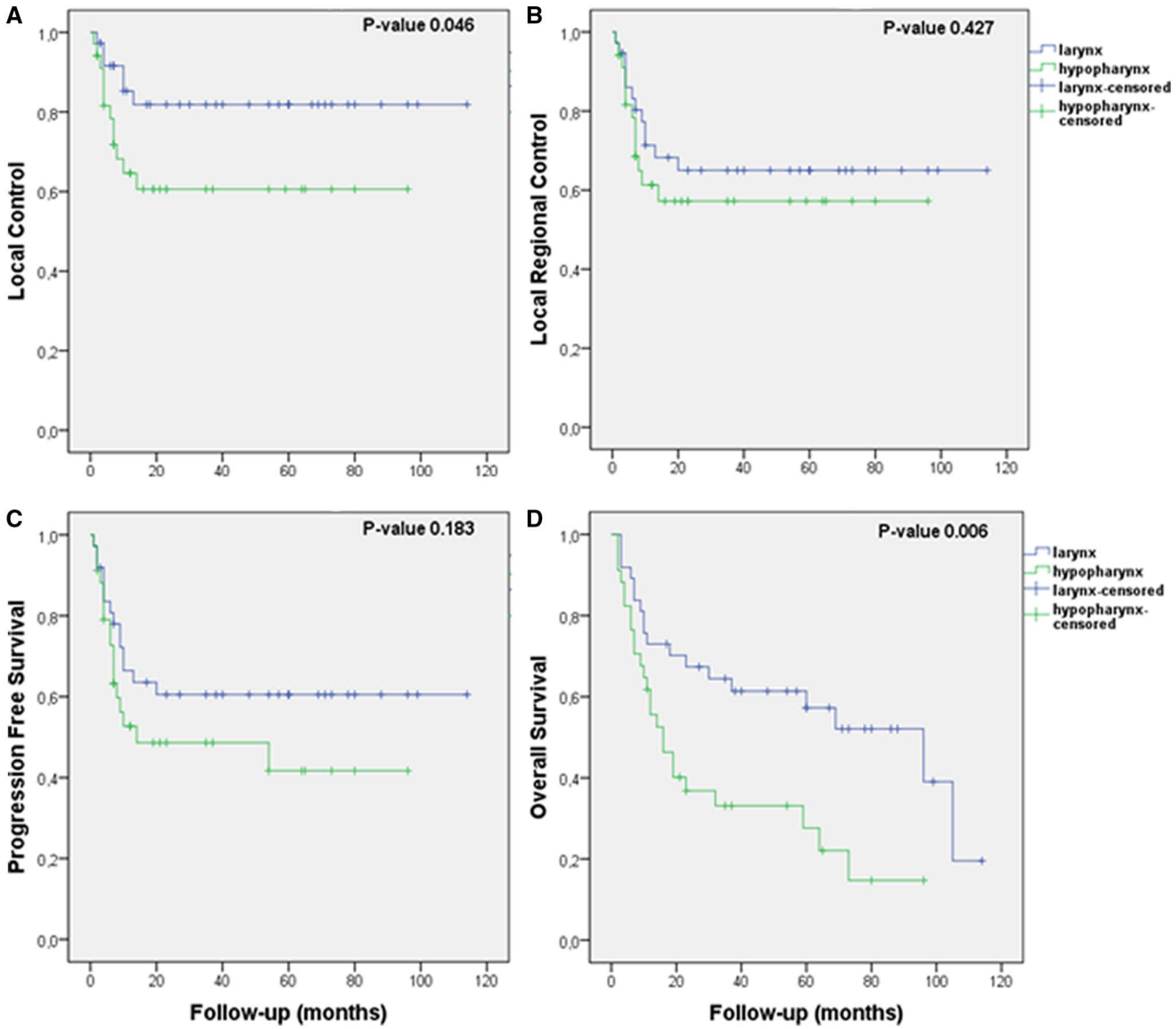

Fig. 2 Kaplan–Meier curves for local control (**a**), loco-regional control (**b**), disease-free survival (**c**), and overall survival (**d**), by tumor sites

shown that pre-treatment tracheotomy was also an independent predictor of worse odds of G-tube removal within 12 months. Our data showed that pre-treatment tracheotomy did not have negative impact on local control or OS in univariate analysis. However, pre-treatment tracheotomy was strongly predictive for persistent tracheostomy after treatment, as tracheotomy decannulation was possible in only one patient with pre-treatment tracheotomy.

With the exception of pre-treatment tracheotomy, poor pre-treatment laryngeal function is not well defined in the literature and little is known about the impact of poor pre-treatment laryngeal function at baseline on oncological and specifically on functional outcomes. In our opinion, extra-laryngeal tumor extension should be defined as a radiological sign of poor pre-treatment laryngeal function, while stridor or airway obstruction needing tracheotomy, repeated aspiration pneumonia, or grade 2–3 dysphagia at baseline as clinical signs of poor pre-treatment laryngeal function. It has been our perception that patients with poor pre-treatment laryngeal function at baseline will end up with poor functional outcomes. The results of this study corroborate this suspicion, as LED-FS is very disappointing after CRT, especially in patients with poor pre-treatment laryngeal function. These patients had significantly worse LED-FS at 5 years compared to those without poor pre-treatment laryngeal function (20% and 74%, respectively, $p = 0.001$). Furthermore, the OS of patients with LED was worse, compared to those without LED (32% and 65%, respectively, $p = 0.041$). In the current study, the presence of clinical signs poor pre-treatment laryngeal function is the only significant predictor

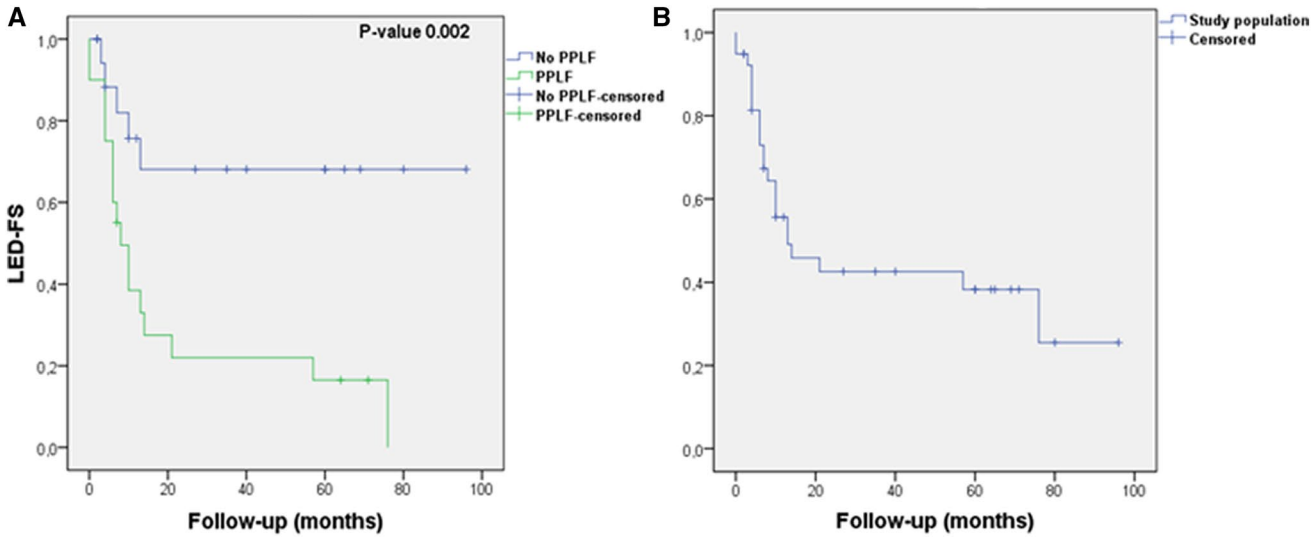

Fig. 3 Kaplan–Meier curves for laryngo-esophageal dysfunction-free survival (LED-FS) of the whole group treated with chemoradiation (right panel) and in patients with or without poor pre-treatment laryngeal function (PPLF) (left panel)

for LED-FS in the multivariate analysis. Therefore, poor pre-treatment laryngeal function might be a marker of worse functional outcomes after organ-preservation approaches and need to be thoroughly discussed with these patients in the setting of shared decision making about whether or not to offer TL instead of organ-preservation therapy. Although organ-preservation treatment is appealing due to the preservation of the speech and swallowing function, the subset of these patients with poor pre-treatment laryngeal function is, in our opinion, not suitable for this strategy with respect to OS. The understandable fear of these patients about ending up with bad QoL scores after TL, especially in speech domains score and social functioning, needs to mitigated, since different studies have shown the opposite [21–23]. The largest series to date reporting on the impact of different treatment demographics on the QoL of head and neck cancer patients showed that feeding tube to be the strongest predictor for lower QoL scores, tracheostomy as a moderate factor, while TL as one of the weaker clinical variables predicting poor QoL scores [22]. Interestingly, the decrements for social functioning scores for TL patients (− 10.1) were of a lesser magnitude than those reported in patients with feeding tube (− 18.1) or tracheotomy (− 16.4). Similarly, laryngectomy patients had less of a decrement in speech scores (− 11.5), compared to the scores in patients with feeding tube (− 24.2) or tracheotomy tube (− 18.9).

The authors recognized the shortcomings of the current study including the retrospective nature with inherent selection bias, the relatively small sample size, and the lack of consensus regarding the definition of functional failure after organ-preservation approaches. Since there are no proper randomized controlled trials conducted to compare primary CRT with TL followed by radiotherapy in T4 tumors, the findings from such, even small, cohort studies are valuable and need to be taken into consideration during the decision making about the best primary treatment options for patients with T4 tumors.

In summary, the current study showed that total laryngectomy resulted in significantly better local control, compared to chemoradiation in patients with T4 laryngeal and hypopharyngeal cancers, however, without significant improvement in overall survival. With regard to the functional outcome of patients treated with chemoradiation, the LED-free survival is very disappointing, especially in patients with poor pre-treatment laryngeal function. These issues should be taken into consideration, as patients are counseled about different primary treatment options. Patients with T4 laryngeal and hypopharyngeal cancer with poor pre-treatment laryngeal function should be primarily treated with total laryngectomy followed by radiotherapy. Chemoradiation remains a second best option and can be considered a reasonable alternative strategy in T4 patients with good laryngeal function at baseline.

Table 2 Univariate and multivariate analyses for LF and OS of the whole group ($n=71$)

Variables	Univariate analysis for LF			Multivariate analysis for LF		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (ref; 45–59) (years)						
59–67	1.54	0.52–4.58	0.441			
67–86	0.73	0.22–2.39	0.601			
Smoking status (ref; stopped)	1.35	0.52–3.48	0.539			
Tumor sites (ref; larynx)	2.58	0.97–6.89	0.058			
Primary treatment (ref; group A)	0.31	0.10–0.94	0.038	0.31	0.10–0.94	0.038
N-stage (ref; N0)	0.82	0.32–2.10	0.67			
Extra-capsular extension (ref; no)	1.39	0.50–3.91	0.53			
Tumor volume (ref; < 35)	1.88	0.62–5.72	0.265			
Systemic therapy (ref; no)	1.75	0.69–4.46	0.237			
Radiological signs of PPLF (ref; no)	0.49	0.19–1.24	0.131			
Clinical signs of PPLF (ref; no)	1.62	0.58–4.54	0.36			
Pre-treatment tracheostomy (ref; no)	0.42	0.10–1.83	0.249			
Variables	Univariate analysis for OS			Multivariate analysis for OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (ref; 45–59) (years)						
59–67	2.67	1.20–5.94	0.016			
67–86	1.65	0.73–3.73	0.23			
Smoking status (ref; stopped)	0.95	0.47–1.91	0.88			
Tumor sites (ref; larynx)	2.32	1.24–4.33	0.008	1.95	1.02–3.73	0.042
Primary treatment (ref; group A)	0.81	0.44–1.48	0.488			
N-stage (ref; N0)	1.84	0.91–3.70	0.087			
Extra-capsular extension (ref; no)	3.13	1.61–6.06	0.001	2.65	1.34–5.24	0.005
Tumor volume (ref; < 35)	1.40	0.72–2.73	0.319			
Systemic therapy (ref; no)	1.49	0.81–2.75	0.196			
Radiological signs of PPLF (ref; no)	0.90	0.48–1.67	0.728			
Clinical signs of PPLF (ref; no)	1.17	0.61–2.23	0.631			
Pre-treatment tracheostomy (ref; no)	1.43	0.73–2.80	0.300			

LF local failure, *OS* overall survival, *HR* hazard ratio, *95% CI* 95% confidence interval, *PPLF* poor pre-treatment laryngeal function

Table 3 Univariate and multivariate analyses for LED of the (chemo)radiation group (39 patients, 22 events)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age (ref; 45–59) (years)						
59–67	1.71	0.37–7.92	0.49			
67–86	0.71	0.14–3.58	0.682			
Smoking status (ref; stopped)	1.22	0.28–5.26	0.791			
Tumor sites (ref; larynx)	1.56	0.43–5.65	0.502			
N-stage (ref; N0)	0.66	0.16–2.77	0.57			
Extra-capsular extension (ref; no)	1.04	0.20–5.41	0.966			
Tumor volume (ref; <35)	5.14	1.30–20.36	0.02			
Systemic therapy (ref; no)	0.66	0.16–2.77	0.57			
Radiological signs of PPLF (ref; no)	1.43	0.40–5.12	0.584			
Clinical signs of PPLF (ref; no)	15.867	3.12–78.32	0.001	15.867	3.12–78.32	0.001
Pre-treatment tracheostomy (ref; no)	4.71	0.50–44.78	0.178			

LED laryngo-esophageal dysfunction, *HR* hazard ratio, *95% CI* 95% confidence interval, *PPLF* poor pre-treatment laryngeal function

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval This article does not contain any experimental study with human participants performed by any of the authors. For this type of work, formal consent is not required due to its retrospective nature.

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