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Laryngology

Organ preservation and oncological outcomes in early laryngeal cancer: a propensity score-based study

Preservazione d'organo ed esiti oncologici nel carcinoma laringeo in stadio iniziale: uno studio basato sul punteggio di propensione

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SUMMARY

Background. The rates of laryngeal preservation according to therapeutic modality in patients with initial laryngeal squamous cell carcinoma (LSCC) are still controversial. This study evaluated the rates of laryngeal preservation in patients who underwent treatment with surgery or radiotherapy.

Methods. This retrospective cohort study evaluated 151 patients with stage I or II LSCC. Ninety-six patients were matched using a propensity-score and outcomes were compared within this group.

Results. Regarding overall, cancer-specific survival and larynx preservation, no differences were observed according to the therapeutic modalities, but patients who underwent radiotherapy had a higher rate of local recurrence than those who underwent surgery. Patients classified as ASA 3 or 4 and treated with radiotherapy showed a tendency of higher risk of larynx loss.

Conclusions. Patients with stage I or II laryngeal tumours can be submitted to surgery or radiotherapy with similar rates of laryngeal preservation.

KEY WORDS: laryngeal neoplasms, laryngeal surgery, laryngeal radiotherapy, organ preservation

RIASSUNTO

Background. *Le percentuali di conservazione della laringe nei diversi trattamenti dei pazienti affetti da carcinoma a cellule squamose della laringe iniziale (LSCC) sono ancora controversi. Questo studio ha valutato i tassi di preservazione laringea nei pazienti sottoposti a trattamento chirurgico o radioterapia.*

Metodi. *Questo studio di coorte retrospettivo ha valutato 151 pazienti con LSCC, stadio I o II. Novantasei pazienti sono stati abbinati utilizzando un punteggio di propensione e i risultati sono stati confrontati all'interno di questo gruppo.*

Risultati. *Per quanto riguarda la sopravvivenza globale, cancro-specifica e la conservazione della laringe, non sono state osservate differenze in base alle modalità terapeutiche, ma i pazienti sottoposti a radioterapia avevano un tasso di recidiva locale più elevato rispetto a quelli sottoposti a intervento chirurgico. Inoltre, i pazienti classificati come ASA 3 o 4 e trattati con radioterapia hanno mostrato una tendenza a un rischio maggiore di perdita della laringe.*

Conclusioni. *I pazienti con tumori laringei in stadio I o II possono essere sottoposti a chirurgia o radioterapia con tassi di conservazione laringea simili.*

PAROLE CHIAVE: *neoplasie laringee, chirurgia laringea, radioterapia laringea, preservazione d'organo*

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Introduction

The treatment of patients with early-stage (stages I and II) laryngeal squamous cell carcinoma (LSCC) is usually based on a single modality, such as surgery or radiotherapy, with similar overall survival rates [1-5]. Studies evaluating organ preservation for these patients have reported controversial results. The systematic review by Warner et al. (2014) documented only one prospective, randomised study comparing surgery and radiotherapy in 234 patients with early-stage disease (all glottic tumours). They demonstrated that patients submitted to radiotherapy showed higher rates of local recurrences than those submitted to surgery. However, no information about organ preservation rates was available for either group, and no significant differences were observed in overall and cancer-specific survival rates [6]. Some meta-analyses and systematic reviews including patients with glottic tumours at clinical stages Tis/T1/T2 and N0 have reported that laryngeal preservation rates are higher in patients who underwent transoral laser surgery than in patients submitted to radiotherapy [7-9]. However, the study by Jones et al. (2004) on 488 larynx cancer patients at clinical stages I and II did not demonstrate a significant difference between overall and cancer-specific survival and local recurrence rates between treatments. The authors also described higher rates of regional recurrence and worse vocal outcomes for patients submitted to surgery than those submitted to radiotherapy; however, they did not evaluate the organ preservation rates of these patients [3]. Most of these studies have some limitations, such as the heterogeneity of treatments, follow-up time, and selection bias due to patient or medical decisions.

Considering these controversial results, the present study evaluated laryngeal preservation rates and survival in patients with laryngeal epidermoid carcinoma at stage I or II treated with surgery (transoral or conventional) or radiotherapy. A propensity score (PS) analysis was performed to reduce the influence of selection bias in outcome analysis.

Materials and methods

Patients, clinical and histopathological characterisation

This is a retrospective cohort study and included 151 patients with cT1N0 or cT2N0 LSCC treated with curative intent from January 1995 to December 2014 at A.C. Camargo Cancer Center (Brazil). The study was approved by the ethics committee (2118/15). Inclusion criteria included previously untreated LSCC at clinical stages I or II and treated with curative intent. Exclusion criteria included patients with other synchronous, prior malignancies in the head and neck and those whose medical records lacked information relevant to the study or a follow-up time less of than 6 months.

All patients were offered both therapeutic modalities. However, no resources for transoral laser surgery were available at our facility until 2014 and many patients refused conventional partial laryngectomy, due to nasoenteral tube, or tracheostomy. Therefore, most were treated with radiotherapy. Patients were followed every 1 to 3 months in the first year, every 2 to 4 months in the second year, every 6 months from 3 to 5 years and thereafter every 12 months. Follow-up was performed with videonasolaryngoscopy or laryngoscopy and computed tomography (CT) or magnetic resonance imaging (MRI) of the neck.

Clinical and pathological data were obtained from medical charts. A review of data from clinical locoregional physical examination, video laryngoscopy and direct laryngoscopy data was carried out to characterise tumour staging. All participants were submitted to MRI or CT of the neck no more than six weeks before initiation of treatment. In addition, participants were submitted to a simple chest X-ray or CT scan for detection of distant metastases or lung cancer. All patients were re-staged in accordance with the Classification of Malignant Tumours of the UICC (8th Edition) [10]. Patients with permanent tracheostomy, recurrent aspiration pneumonia in the last year of follow-up, percutaneous gastrostomy, or nasoenteral tube were considered with loss of laryngeal function.

To reduce selection bias from non-random allocation to different treatments, we used propensity-score matching. The variable used for propensity-score calculation was clinical stage and treatment. Patients were matched according to the nearest-neighbor algorithm with a 0.02 caliper. The p-value for statistical significance was 5%. Survival curves and laryngo-oesophageal dysfunction were analysed using the Kaplan Meier method, assessing statistical significance between groups with the log-rank test. Cox regression was used to estimate the risk factors for clinical outcomes, with its influence evaluated by hazard ratio (HR) and 95% confidence intervals. Statistical analysis was performed using SPSS software (v. 21.0; SPSS, Chicago, IL, USA).

Results

Clinical data

According to inclusion and exclusion criteria, 151 patients were included in the study. Among these, 124 patients were men (82%) and the median age was 61 years (range 22-77 years). The majority of the patients (n = 135; 89%) had previous tobacco exposure and 92 (58.5%) were consumers of alcoholic beverages. Sixty-six patients (45.2%) had comorbidities at diagnosis, with hypertension (n = 14; 9.2%)

and type II diabetes (n = 7; 4.2%) being the most frequent. Thirty-five patients (41.2%) were in the normal weight range considering body mass index (BMI) and most were classified as ASA 2 (n = 72; 76.6%). The follow-up period ranged from 6 to 276 months (median of 55 months). Twenty-three (15.2%) patients were lost to follow up, with a median time of 34 months (ranging from 18 days to 97 months). There were no significant differences between patients lost to follow-up according to treatment.

Among these patients, 96 were matched after PS analysis. These groups were used to evaluate the association of treatment modality with clinical outcomes and functional larynx preservation rates.

Of the 48 patients submitted to surgery, 37 (77,1%) underwent a conventional partial laryngectomy, 12 (25%) underwent frontolateral partial laryngectomy, 11 (22.9%) transoral endoscopic surgery resection and 39 (81,2)%) had resection with free margins. After pathological analysis, three of 18 cT1a patients were upstaged to pT2. From 28 tumours staged as cT2, six (21.4%) were staged as pT1 and six (21.4%) as pT3 due to paraglottic space invasion. No patient with a transglottic tumour was submitted to surgery. Among these patients, eight (16.6%) underwent postoperative adjuvant radiotherapy by positive margins.

In patients submitted to radiotherapy, the final dose ranged from 51.7 to 70.4 Gy (median, 66 Gy) for cT1a patients, 50.5 to 70 Gy (median, 64.2 Gy) for cT1b patients and 54 to 74.4 Gy (median, 69.7 Gy) in cT2 patients. Radiotherapy treatment time was 51 days, ranging from 26 to 85 days. Most patients presented acute side effects (n = 45; 95.8%), with radiodermatitis grades 1 or 2 being the most frequent, but only four (3.9%) patients discontinued the treatment due to complications.

Table I depicts the characteristics of all patients and the study sample after selection, with higher prevalence of smokers, alcohol consumers and supraglottic tumors in the group submitted to surgery, and more glottic tumours in the group submitted to radiotherapy. Tumour extension to the anterior commissure was more prevalent in the radiotherapy group. No other significant differences were observed between groups.

Overall survival and cancer-specific survival

The overall survival rate was 78.6% at 5 years, and 64.2% at 10 years. No significant difference in overall survival was observed between groups. The overall survival rate at 5 years was 78.9% for patients with glottic tumors and 67.9% for patients with other tumour locations (p = 0.59); 80.9% for patients with clinical stage I and 70.4% for clinical stage II (p = 0.61); it was 79.4% for tumours with staging cT1a, 87.5% cT1b and 73% cT2 (p = 0.72). In relation to treatment, the overall survival rates of patients submitted to surgery and radiotherapy were 70.4% and 77.6%, respectively (p = 0.43) (Fig. 1).

Cancer-specific survival (CSS) rates at 5 and 10 years were 89.7% and 83.2%, respectively. The CSS rate at 5 years was 85.9% for patients with glottic tumours and 87.6% for patients with other tumour locations (p = 0.61); 87.1% for patients with clinical stage I and 88.2% for patients with clinical stage II (p = 0.47); 87.3% for tumors with staging cT1a, 70% cT1b and 88.2% cT2 (p = 0.64). In relation to treatment, the CSS rates in patients submitted to surgery and radiotherapy were 89.2% and 86.7%, respectively (p = 0.78) (Fig. 2). Table II shows the estimates of the pa-

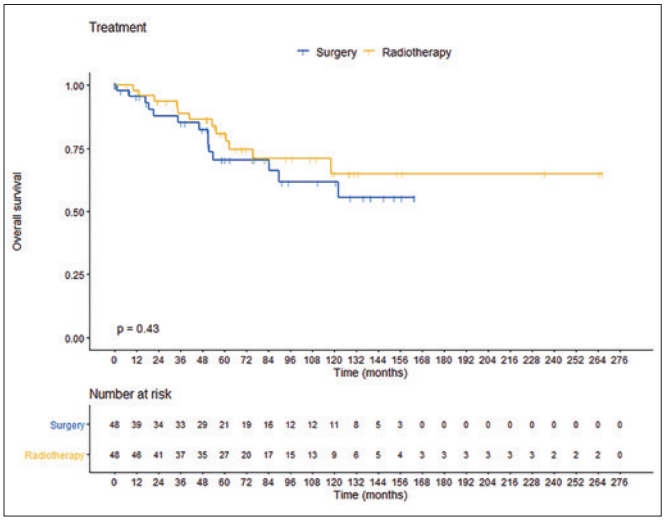

Figure 1. Overall survival by treatment.

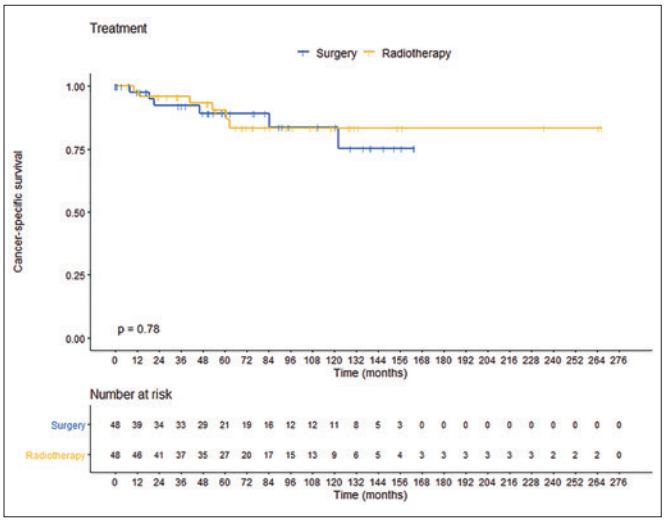

Figure 2. Cancer-specific survival by treatment.

Table I. Demographic variables related to the patient and tumour extension by categories and frequencies according to the treatment performed before and after the propensity score.

Variables	Categories	Before propensity score			After propensity score		
		Surgery Freq. (%)	Radiotherapy Freq. (%)	p*	Surgery Freq. (%)	Radiotherapy Freq. (%)	p
Gender	Female	5 (10.4%)	22 (21.4%)	0.160	5 (10.4%)	11 (22.9%)	0.170
	Male	43 (89.6%)	81 (78.6%)		43 (89.6%)	37 (77.1)	
Age (years)	≤ 70	39 (81.3%)	73 (70.9%)	0.247	39 (81.3%)	39 (81.3%)	1
	> 70	9 (18.8%)	30 (29.1%)		9 (18.8%)	9 (18.8%)	
Education level	No graduation	32 (82.1%)	61 (75.4%)	0.140	32 (82.1%)	27 (72.9%)	0.198
	Graduation or more	7 (17.9%)	21 (25.6%)		7 (17.9%)	10 (27.10%)	
Race	White	43 (89.6%)	97 (94.2%)	0.512	43 (89.6%)	46 (95.8%)	0.488
	No white	5 (10.4%)	6 (5.8%)		3 (6.3%)	1 (2.1%)	
Smoking	No	0 (0.0%)	16 (16.3%)	0.003	0 (0.0%)	7 (15.2%)	0.006
	Yes	36 (75.0%)	50 (51.0%)		36 (75.0%)	23 (50.0%)	
	Ex-smoker	12 (25.0%)	32 (32.7%)		12 (21.2%)	16 (34.8%)	
Alcohol use	No	12 (25.0%)	47 (50.0%)	0.005	12 (25.0%)	21 (47.7%)	0.021
	Yes	29 (60.4%)	43 (45.7%)		29 (60.4%)	22 (50.0%)	
	Ex-drinker	7 (14.6%)	4 (4.3%)		7 (14.6%)	1 (2.3%)	
Comorbidities	No	20 (42.6%)	60 (60.6%)	0.062	20 (42.6%)	28 (59.6%)	0.074
	Yes	27 (57.4%)	39 (39.4%)		27 (57.4%)	19 (40.4%)	
BMI**	Underweight	1 (3.2%)	1 (1.9%)	0.612	1 (3.2%)	1 (4.5%)	0.609
	Heathy	15 (48.4%)	20 (37.0%)		15 (48.4%)	7 (31.8%)	
	Excess body weight	11 (35.5%)	27 (50.0%)		11 (35.5%)	12 (54.5%)	
	Obese	4 (12.9%)	6 (11.2%)		4 (12.9%)	2 (9.1%)	
ASA***	1	1 (2.4%)	4 (7.5%)	0.622	1 (2.4%)	2 (10.0%)	0.409
	2	34 (82.9%)	38t (71.7%)		34 (82.9%)	14 (70.0%)	
	3	5 (12.2%)	9 (17.0%)		5 (12.2%)	4 (20.0%)	
	4	1 (2.4%)	2 (3.8%)		1 (2.4%)	0 (0.0%)	
Tumour site	Glottic	22 (45.8%)	90 (87.4%)	< 0.001	22 (45.8%)	39 (81.3%)	0.03
	Supraglottic	26 (54.2%)	11 (10.7%)		26 (54.2%)	7 (14.6%)	
	Transglottic	0 (0.0%)	2 (1.9%)		0 (0.0%)	2 (4.2%)	
Clinical tumour stage	T1a	18 (37.0%)	49 (47.6%)	0.001	18 (37.%)	14 (29.2%)	0.287
	T1b	2 (4.2%)	23 (22.3%)		2 (4.2%)	6 (12.5%)	
	T2	28 (58.3%)	31 (30.1%)		28 (58.3%)	28 (58.3%)	
Anterior commissure	No	45 (93.8%)	75 (72.8%)	0.006	45 (93.8%)	37 (77.1%)	0.04
	Yes	3 (6.3%)	28 (27.2%)		3 (6.3%)	11 (22.9%)	
Clinical stage	I	20 (41.7%)	72 (69.9%)	0.002	20 (41.7%)	20 (41.7%)	0.999
	II	28 (58.3%)	31 (30.1%)		28 (58.3%)	28 (58.3%)	
Previous tracheostomy	No	48 (100.0%)	101 (98.1%)	1.00	48 (100%)	46 (95.8%)	0.247
	Yes	0 (0%)	2 (1.19%)		0 (0.0%)	2 (4.2%)	

** Chi-square test. ** Body mass index *** Physical Status Classification System of American Society of Anesthesiologists.*

Table II. Estimates of the parameters of the Cox regression model for the outcome of overall and cancer-specific survival.

Variables	Categories	Overall survival				Cancer-specific			
		No event (n = 70)	Event (n = 26)	HR	p	No event (n = 84)	Event (n = 12)	HR	p
Gender	Female	13 (18.6%)	3 (11.5%)	Ref		15 (17.9%)	1 (8.3%)	Ref	0.385
	Male	57 (81.4%)	23 (88.5%)	1.712	0.381	69 (82.1%)	11 (91.7%)	2.478	
Age (years)	≤ 70	56 (80%)	22 (84.6%)	Ref		67 (79.8%)	11 (91.7%)	Ref	0.377
	> 70	14 (20%)	4 (15.4%)	0.784	0.655	17 (20.2%)	1 (8.3%)	0.398	
Race	White	65 (92.9%)	24 (92.3%)	Ref		53 (80.3%)	6 (60.0%)	Ref	0.152
	No white	5 (7.1%)	2 (7.7%)	2.359	0.250	13 (19.7%)	4 (40.0%)	2.550	
Education degree level	No graduation	44 (78.6%)	15 (75%)	Ref		77 (91.7%)	12 (100%)		
	Graduation or more	12 (21.4%)	5 (25%)	1.247	0.670	7 (8.3%)	0 (0.0%)	NE*	
Smoking	No	6 (8.8%)	1 (3.8%)	Ref		7 (8.5%)	0 (0.0%)	NE*	
	Yes	41 (60.3%)	18 (69.2%)	2.495	0.374	50 (61.0%)	9 (75.0%)	NE*	
	Ex-smoker	21 (30.9%)	7 (26.9%)	2.128	0.480	25 (30.5%)	3 (25.0%)	NE*	
Alcohol use	No	24 (36.4%)	9 (34.6%)	Ref		28 (35.0%)	5 (41.7%)	NE*	
	Yes	38 (57.6%)	13 (50%)	1.071	0.874	44 (55.0%)	7 (58.3%)	NE*	
	Ex-drinker	4 (6.1%)	4 (15.4%)	3.041	0.066	8 (10.0%)	0 (0.0%)	NE*	
Comorbidities	No	35 (51.5%)	13 (50%)	Ref		42 (51.2%)	6 (50.0%)	Ref	0.688
	Yes	33 (48.5%)	13 (50%)	0.792	0.553	40 (48.8%)	6 (50.0%)	0.793	
BMI**	No heathy	24 (57.1%)	7 (63.6%)	Ref		28 (58.3%)	3 (60.0%)		0.933
	Heathy	18 (42.9%)	4 (36.4%)	0.993	0.992	20 (41.7%)	2 (40.0%)	1.081	
ASA***	1 or 2	39 (84.8%)	12 (80%)	Ref		45 (83.3%)	6 (85.7%)	Ref	0.979
	3 or 4	7 (15.2%)	3 (20%)	1.386	0.617	9 (16.7%)	1 (14.3%)	0.972	
Tumour site	No glottic	23 (32.9%)	12 (46.2%)	Ref		31 (36.9%)	4 (33.3%)	Ref	0.616
	Glottic	47 (67.1%)	14 (53.8%)	0.808	0.588	53 (63.1%)	8 (66.7%)	1.359	
Clinical tumour stage	1a	26 (37.1%)	6 (23.1%)	Ref		28 (33.3%)	4 (33.3%)	Ref	0.586
	1b	5 (7.1%)	3 (11.5%)	1.599	0.507	6 (7.1%)	2 (16.7%)	1.604	0.669
	2	39 (55.7%)	17 (65.4%)	1.412	0.468	50 (59.5%)	6 (50.0%)	0.759	
Clinical stage	I	31 (44.3%)	9 (34.6%)	Ref		34 (40.5%)	6 (50.0%)	Ref	0.478
	II	39 (55.7%)	17 (65.4%)	1.236	0.608	50 (59.5%)	6 (50.0%)	0.664	
Anterior commissure	No	61 (87.1%)	21 (80.8%)	Ref		72 (85.7%)	10 (83.3%)	Ref	0.934
	Yes	9 (12.9%)	5 (19.2%)	1.298	0.601	12 (14.3%)	2 (16.7%)	1.066	
Treatment	Surgery	34 (48.6%)	14 (53.8%)	Ref		42 (50.0%)	6 (50.0%)	Ref	0.784
	Radiotherapy	36 (51.4%)	12 (46.2%)	0.736	0.436	42 (50.0%)	6 (50.0%)	0.854	

** There are no numbers to evaluate ** Body mass index. *** Physical Status Classification System of American Society of Anesthesiologists.*

rameters of the Cox regression model for the outcome of overall and cancer-specific survival and Figure 2 shows CSS by treatment.

Local recurrence-free survival

The local recurrence-free survival (LRFS) rate was 76.5% at 5 years, and 67.6% at 10 years. The recurrence rate was 12.5% after surgery and 37.5% after radiotherapy (p = 0.021). Patients classified as ASA 3 or 4 with glottic tumours who underwent radiotherapy had a higher risk of local recurrences. Conversely, no significance differences were seen for gender, tobacco and alcohol exposure, pathological classification and tumour extension for anterior commissure. The LRFS rate was 76.5% for patients with glottic tumours and 83.7% for patients with tumours at other locations (p = 0.048); 79.3% for patients with clinical stage I disease and 79.3% for patients with clinical stage II (p = 0.53); and 79.2% for tumours staged cT1a, 74.3% cT1b and 79.2% cT2 (p = 0.73). With respect to treatment,

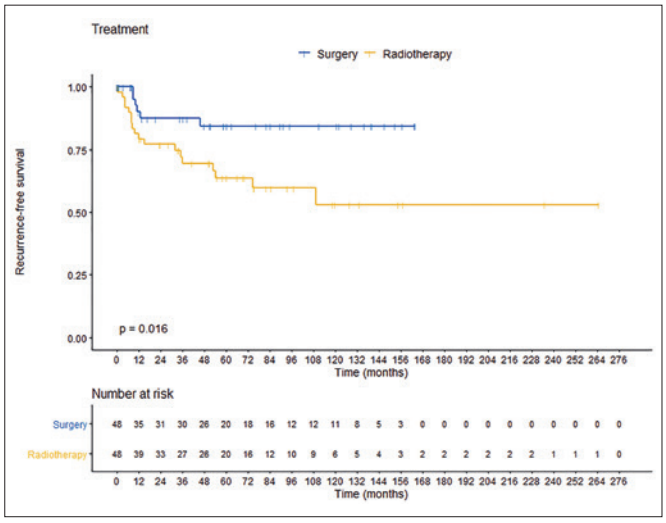

Figure 3. Local recurrence-free survival by treatment.

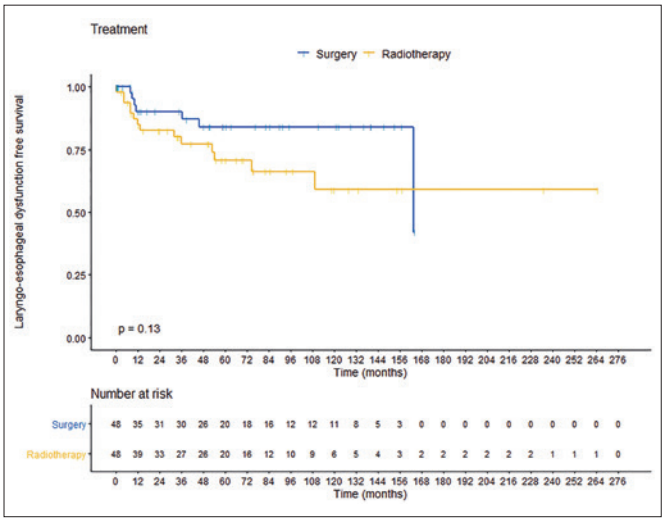

Figure 4. Laryngo-oesophageal dysfunction free survival by treatment.

LRFS rates of patients submitted to surgery and radiotherapy were 84.3% and 63.6%, respectively (p = 0.016) (Fig. 3, Tab. III).

Among patients who underwent surgery, six had local recurrence, with one frontolateral partial laryngectomy and three total laryngectomies with neck dissection and adjuvant radiotherapy as salvage procedures. Chemoradiotherapy as an organ preservation strategy after local recurrence was performed in two patients. In patients treated with radiotherapy, 18 presented local recurrence, 14 were submitted to total laryngectomy with neck dissection, two to frontolateral laryngectomy, one supracricoid laryngectomy and one to endoscopic transoral surgery. Local recurrence rates were higher in patients with supraglottic tumours staged by cT2 and treated with radiotherapy (Tab. IV).

Laryngeal preservation

The laryngeal preservation rate was 78.2%. No correlation was found between the probability of laryngeal preservation and the variables analysed, although patients with ASA classification 3 or 4 who underwent radiotherapy presented a tendency towards higher risk of laryngeal loss, but without statistical significance. Among the 48 patients who underwent surgery, seven had a non-functional larynx at the end of follow-up: three were submitted to salvage total laryngectomy, two presented chronic aspiration and had a percutaneous gastrostomy and two had permanent tracheostomy due to laryngeal stenosis. In the patients treated by radiotherapy, except for 14 who underwent salvage total laryngectomy, the remaining had a functioning larynx at the time of assessment. Table V shows the estimates of the parameters of the simple logistic regression model for laryngeal preservation and Figure 4 shows laryngo-oesophageal dysfunction-free survival curves.

Discussion

The treatment of patients with LSCC at clinical stages cT1N0 or cT2N0 depends on various factors such as availability of infrastructure for each treatment modality, the patient's physical condition, multidisciplinary team preferences and patient choice, especially regarding voice preservation together with characteristics of the tumours, and especially its primary location. Thus, random prospective studies for this group of patients have not been developed, with the exception of Ogol'tsova et al. (1990) cited by Warner et al. (2014), which has some methodological issues.

Data from the literature and previous analysis of this study showed a trend towards the use of radiotherapy in patients with glottic tumours and the use of surgery in patients with supraglottic tumours or stage cT2N0. Thus, the propensity score was used to reduce the impact of selection bias in outcomes. This methodology has been largely used in medicine and is considered a good option for randomised prospective clinical studies [11].

OS and CSS had no significant association with clinical variables. Although Guimarães et al. (2018) described a higher OS and CSS rates for patients with glottic tumours cTis/cT1a treated with surgery compared to those treated with radiotherapy. Similar results were found in the study by Vaculik et al. (2019) on patients with cT1 stage glottic tumours. In contrast, the systematic reviews by Yoo et al. (2014) and Warner et al. (2014) found no significant differ-

Table III. Estimates of the parameters of the Cox regression model for the outcome of local recurrence-free survival.

Variables	Categories	Local recurrence		HR	CI (95%)		p
		No event (n = 72)	Event (n = 24)		Lower	Higher	
Gender	Female	13 (18.1%)	3 (12.5%)	Ref			
	Male	59 (81.9%)	21 (87.5%)	1.594	0.475	5.347	0.450
Age (years)	≤70	55 (76.4%)	23 (95.8%)	Ref			
	> 70	17 (23.6%)	1 (4.2%)	0.164	0.022	1.217	0.077
Race	White	65 (90.3%)	24 (100%)				
	No white	7 (9.7%)	0 (0.0%)	NA			
Education degree level	No graduation	43 (76.8%)	16 (80.%)	Ref			
	Graduation or more	13 (23.2%)	4 (20.0%)	0.866	0.289	2.595	0.798
Smoking	No	6 (8.6%)	1 (4.2%)	Ref			
	Yes	44 (62.9%)	15 (62.5%)	2.012	0.265	15.251	0.499
	Ex-smoker	20 (28.6%)	8 (33.3%)	2.233	0.279	17.883	0.449
Alcohol use	No	25 (36.8%)	8 (33.3%)	Ref			
	Yes	36 (52.9%)	15 (62.5%)	1.406	0.596	3.320	0.436
	Ex-drinker	7 (10.3%)	1 (4.2%)	0.734	0.091	5.890	0.771
Comorbidities	No	35 (50.0%)	13 (54.2%)	Ref			
	Yes	35 (50.0%)	11 (45.8%)	0.663	0.296	1.483	0.317
BMI*	No heathy	25 (59.5%)	6 (54.5%)	Ref			
	Heathy	17 (40.5%)	5 (45.5%)	1.163	0.354	3.821	0.803
ASA**	1 or 2	42 (89.4%)	9 (64.3%)	Ref			
	3 or 4	5 (10.6%)	5 (35.7%)	3.092	1.030	9.285	0.044
Tumour site	No glottic	30 (41.7%)	5 (20.8%)	Ref			
	Glottic	42 (58.3%)	19 (79.2%)	2.705	1.008	7.261	0.048
Clinical tumour stage	1a	23 (31.9%)	9 (37.5%)	Ref			
	1b	6 (8.3%)	2 (8.3%)	0.695	0.150	3.219	0.642
	2	43 (59.7%)	13 (54.2%)	0.718	0.306	1.681	0.445
Clinical stage	I	29 (40.3%)	11 (45.8%)	Ref			
	II	43 (59.7%)	13 (54.2%)	0.775	0.347	1.731	0.534
Anterior commissure	No	62 (86.1%)	20 (83.3%)	Ref			
	Yes	10 (13.9%)	4 (16.7%)	1.021	0.349	2.991	0.969
Treatment	Surgery	42 (58.3%)	6 (25.0%)	Ref			
	Radiotherapy	30 (41.7%)	18 (75.0%)	2.967	1.177	7.479	0.016

** Body mass index. ** Physical Status Classification System of American Society of Anesthesiologists.*

Table IV. Local recurrence-free survival estimates at 5 years by tumour location and staging according to treatment.

Variables	Categories		Treatment		p
			Surgery	Radiotherapy	
Tumour site/Stage	Glottic	T1	76.5%	63.2%	0.949
		T2	80.0%	65.0%	0.286
	Supraglottic	T1	100.0%	100.0%	1
		T2	95.7%	50.0%	0.04

Table V. Estimates of parameters of the simple logistic regression model for laryngeal preservation.

Variables	Categories	Laryngeal preservation		p		95% CI		p
		No (n = 21)	Yes (n = 75)		OR	Lower	Higher	
Gender	Female	2 (9.5%)	14 (18.7%)	0.510*	Ref			
	Male	19 (90.5%)	61 (81.3%)		0.459	0.096	2.201	0.330
Age	≤ 70	18 (85.7%)	60 (80.0%)	0.755	Ref			
	> 70	3 (14.3%)	15 (20.0%)		1.500	0.390	5.768	0.555
Race	White	21 (100%)	68 (90.7%)	0.341*				
	No White	0 (0.0%)	7 (9.3%)		NA			
Education degree level	No graduation	15 (78.9%)	44 (77.2%)	0.999*	Ref			
	Graduation or more	4 (21.1%)	13 (22.8%)		1.108	0.313	3.924	0.874
Smoking	No	0 (0.0%)	7 (9.6%)	0.334***	NA			
	Yes	14 (66.7%)	45 (61.6%)		NA			
	Ex-smoker	7 (33.3%)	21 (28.8%)		NA			
Alcohol use	No	8 (38.1%)	25 (35.2%)	0.765***	Ref			
	Yes	12 (57.1%)	39 (54.9%)		1.040	0.373	2.901	0.940
	Ex-drinker	1 (4.8%)	7 (9.9%)		2.240	0.238	21.072	0.481
Comorbidities	No	10 (47.6%)	38 (52.1%)	0.912**	Ref			
	Yes	11 (52.4%)	35 (47.9%)		0.837	0.317	2.213	0.720
BMI**	No heathy	10 (76.9%)	21 (52.5%)	0.219**	Ref			
	Heathy	3 (23.1%)	19 (47.5%)		3.016	0.721	12.624	0.131
ASA***	1 or 2	10 (66.7%)	41 (89.1%)	0.101*	Ref			
	3 or 4	5 (33.3%)	5 (10.9%)		0.244	0.059	1.008	0.051
Tumour site	No glottic	5 (23.8%)	30 (40.0%)	0.269**	Ref			
	Glottic	16 (76.2%)	45 (60.0%)		0.469	0.155	1.416	0.179
Anterior commissure	No	16 (76.2%)	66 (88%)	0.180*	Ref			
	Yes	5 (23.8%)	9 (12%)		0.436	0.129	1.481	0.184
cT	1a	5 (23.8%)	27 (36.0%)	0.380***	Ref			
	1b	3 (14.3%)	5 (6.7%)		0.309	0.055	1.724	0.180
	2	13 (61.9%)	43 (57.3%)		0.613	0.196	1.912	0.399
Treatment	Surgery	7 (33.3%)	41 (54.7%)	0.139**	Ref			
	Radiotherapy	14 (66.7%)	34 (45.3%)		0.415	0.150	1.144	0.089

*NA: Not available due to insufficient number for calculation OR. * Fisher exact test. ** Chi-square test with continuity correction. *** Chi-square test. **** Body mass index. ***** Physical Status Classification System of American Society of Anesthesiologists.*

ences in OS and CSS between surgery and radiotherapy in patients with early laryngeal cancer.

The local recurrence-free survival rate was lower in patients classified as ASA 3 or 4, with glottic tumours, and submitted to radiotherapy. These patients were preferably treated with radiotherapy because of the high risk of surgery and to improve the quality of voice preservation, respectively. Kowalski et al. (1993) evaluated 145 patients treated between 1954 and 1990 and described a higher rate of local recurrences in patients undergoing radiotherapy (29.5%) compared to those who underwent surgery (10%). Of course, differences in technology in diagnosing and treating these tumors has a definite impact on clinical outcomes.

The laryngeal preservation rate has been controversially reported in the literature. Some authors demonstrated higher rates of preservation in patients who underwent surgery [8,12-15], whereas others demonstrated that radiotherapy shows similar results to surgery with even better functional results [3,16,17]. In the present study, we observed a higher tendency for laryngeal preservation in patients who underwent surgery compared with those who underwent radiotherapy, although the difference was not statistically significant. Compared with surgery, radiotherapy showed higher rates of local recurrence (12.5 *vs* 37.5%) and 22% were candidates for salvage partial laryngectomy. In this scenario, partial laryngectomy presented high

rates of local complications, longer decannulation and enteral feeding times, and a higher risk of second recurrences. Therefore, patients must be carefully selected for this treatment modality [18,19].

Long-term laryngeal preservation in patients who had local recurrence is dependent on the patient's physical condition, the possibility of proper follow up and the experience of the multidisciplinary team in performing partial salvage laryngectomy [20,21]. These factors should also be considered when choosing initial treatment. Furthermore, the initial therapeutic choice should also consider the outcome of the salvage treatment.

In pathological staging, 16.7% of cT1a tumours were restaged for pT2; of 28 cT2 tumours, 17 (60.7%) had a different final pathological staging: six were pT1a (21.4%), six were pT3 (21.4%) and five changed to pT4a (17.8%) due to laryngeal cartilage in the anterior commissure invasion (not detected on previous CT for pre-surgery staging). Therefore, the higher incidence of local recurrence in patients who underwent radiotherapy than in those who underwent surgery could be related not only to biological factors, but also to inappropriate clinical tumour stage. Thus, accurate clinical staging is essential for adequate treatment, especially in cT2.

Regarding the radiotherapy group, the rate of radiotherapy interruption was only 3.9%, and patients were treated with doses of radiation described in the literature: a median of 66 Gy in cT1a tumours, 64.2 Gy in cT1b tumours and 69.7 Gy in cT2 tumours [22,23].

Despite the use of the PS method to match patients according to treatment modality, this study has limitations inherent to the retrospective cohort design. Unlike randomised prospective studies where groups are matched by known and unknown variables, the propensity score method does not allow matching by all characteristics. This study also demonstrated additional significant differences between the groups even after PS matching. A high prevalence of alcohol and tobacco consumers and cT2N0 tumours was observed in the surgery group, whereas the group treated with radiotherapy had a higher prevalence of cT1aN0 glottic tumors. These characteristics may indicate a bias in group selection. These types of biases have been a limitation in a variety of retrospective studies [24] in comparison to randomised prospective trials [25]. The presence of missing values for some variables is also a limitation, such as the possibility of adequate exposure of the larynx in patients who underwent radiotherapy, whether the therapeutic choice was made mainly by the medical team or the patient, lack of information regarding final vocal quality, and treatment costs according to therapeutic modality.

Conclusions

Patients with LSCC at clinical stages I/II treated with surgery or radiotherapy at a reference oncology centre with multidisciplinary teams and regular post-treatment follow-up seems to have similar overall and cancer-specific survival. However, even in this scenario, treatment with radiotherapy is associated with a higher risk of local recurrence, not only for possible inappropriate clinical staging, but also due to biological factors related to radiotherapy resistance. Thus, the appropriate follow-up and expertise of performing salvage partial laryngectomy after local recurrence after radiotherapy is essential to achieve similar laryngeal preservation rates.

References

1 Kowalski LP, Batista MB, Santos CR, et al. Prognostic factors in glottic carcinoma clinical stage I and II treated by surgery or radiotherapy. Am J Otolaryngol 1993;14:122-127.

2 Ansarin M, Zabrodsky M, Bianchi L, et al. Endoscopic CO2 laser surgery for early glottic cancer in patients who are candidates for radiotherapy: results of a prospective nonrandomized study. Head Neck 2006;28:121-125. https://doi.org/10.1002/hed.20301

3 Jones DA, Mendenhall CM, Kirwan J, et al. Radiation therapy for management of t1-t2 glottic cancer at a private practice. Am J Clin Oncol 2010;33:587-590. https://doi.org/10.1097/COC.0b013e3181beaab0

4 Thomas L, Drinnan M, Natesh B, et al. Open conservation partial laryngectomy for laryngeal cancer: a systematic review of English language literature. Cancer Treat Rev 2012;38:203-211. https://doi.org/10.1016/j.ctrv.2011.05.010

5 O'Hara J, Markey A, Homer JJ. Transoral laser surgery versus radiotherapy for tumour stage 1a or 1b glottic squamous cell carcinoma: systematic review of local control outcomes. J Laryngol Otol 2013;127:732-738. https://doi.org/10.1017/S0022215113001400

6 Warner L, Chudasama J, Kelly CG, et al. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. Cochrane Database Syst Rev 2014;12:CD002027. https://doi.org/ 10.1002/14651858.CD002027

7 Yoo J, Lacchetti C, Hammond JA, et al. Role of endolaryngeal surgery (with or without laser) versus radiotherapy in the management of early (T1) glottic cancer: a systematic review. Head Neck 2014;36:1807-1819. https://doi.org/10.1002/hed.23504

8 Hendriksma M, Heijnen BJ, Sjögren EV. Oncologic and functional outcomes of patients treated with transoral CO2 laser microsurgery or radiotherapy for T2 glottic carcinoma: a systematic review of the literature. Curr Opin Otolaryngol Head Neck Surg 2018;26:84-93. https://doi.org/10.1097/MOO.0000000000000438.

9 Guimarães AV, Dedivitis RA, Matos LL, et al. Comparison between transoral laser surgery and radiotherapy in the treatment of early glottic cancer: a systematic review and meta-analysis. Sci Rep 2018;8:11900. https://doi.org/10.1038/s41598-018-30218-x

10 Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Manual. Eighth edition. New York: Springer; 2017. Larynx; pp. 46-64.

11 Loux TM. Randomization, matching, and propensity scores in the design and analysis of experimental studies with measured baseline covariates. Stat Med 2015;34:558-570. https://doi.org/10.1002/sim.6361

[12] Abdurehim Y, Hua Z, Yasin Y, et al. Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of T1a glottic cancer. Head Neck 2012;34:23-33. https://doi.org/10.1002/hed.21686

[13] Succo G, Crosetti E, Bertolin A, et al. Benefits and drawbacks of open partial horizontal laryngectomies. Part A: early-to intermediate-stage glottic carcinoma. Head Neck 2016;38:333-340. https://doi.org/10.1002/hed.23997

[14] Ansarin M, Cattaneo A, De Benedetto L, et al. Retrospective analysis of factors influencing oncologic outcome in 590 patients with early-intermediate glottic cancer treated by transoral laser microsurgery. Head Neck 2017;39:71-81. https://doi.org/10.1002/hed.24534

[15] Vaculik MF, MacKay CA, Taylor SM, et al. Systematic review and meta-analysis of T1 glottic cancer outcomes comparing CO(2) transoral laser microsurgery and radiotherapy. J Otolaryngol Head Neck Surg 2019;48:44. https://doi.org/10.1186/s40463-019-0367-2

[16] Rosier JF, Grégoire V, Counoy H, et al. Comparison of external radiotherapy, laser microsurgery and partial laryngectomy for the treatment of T1N0M0 glottic carcinomas: a retrospective evaluation. Radiother Oncol 1998;48:175-183. https://doi.org/10.1016/s0167-8140(98)00058-9

[17] Aaltonen LM, Rautiainen N, Sellman J, et al. Voice quality after treatment of early vocal cord cancer: a randomized trial comparing laser surgery with radiation therapy. Int J Radiat Oncol Biol Phys 2014;90:255-260. https://doi.org/10.1016/j.ijrobp.2014.06.032

[18] Locatello LG, Cannavicci A, Gallo O. Prognostic impact of initial treatment in surgically salvaged recurrences of early glottic cancer. Laryngoscope 2019;129:2328-2333. https://doi.org/10.1002/lary.27702

[19] Bertolin A, Lionello M, Ghizzo M, et al. Salvage open partial horizontal laryngectomy after failed radiotherapy: a multicentric study. Laryngoscope 2020;130:431-436. https://doi.org/10.1002/lary.27959

[20] Pontes P, Brasil Ode O, Amorim Filho Fde S, et al. Radiotherapy for early glottic cancer and salvage surgery after recurrence. Braz J Otorhinolaryngol 2011;77:299-302. https://doi.org/10.1590/s1808-86942011000300005

[21] Agra IM, Ferlito A, Takes RP, et al. Diagnosis and treatment of recurrent laryngeal cancer following initial nonsurgical therapy. Head Neck 2012;34:727-735. https://doi.org/10.1002/hed.21739

[22] Mendenhall WM, Parsons JT, Stringer SP, et al. Management of Tis, T1, and T2 squamous cell carcinoma of the glottic larynx. Am J Otolaryngol 1994;15:250-257. https://doi.org/10.1016/0196-0709(94)90091-4

[23] Franchin G, Minatel E, Gobitti C, et al. Radiation treatment of glottic squamous cell carcinoma, stage I and II: analysis of factors affecting prognosis. Int J Radiat Oncol Biol Phys 1998;40:541-548. https://doi.org/10.1016/s0360-3016(97)00768-2

[24] Enarson DA, Kennedy SM, Miller DL. Choosing a research study design and selecting a population to study. Int J Tuberc Lung Dis 2004;8:1151-1156.

[25] Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 2014;9:MR000034. https://doi.org/10.1002/14651858.MR000034