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RESEARCH PAPER

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Oncological outcomes of surgical management for T2N0M0 glottic laryngeal squamous cell carcinoma

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Abstract

Objectives: The research aimed to evaluate the clinical treatment outcomes of T2N0M0 glottic laryngeal squamous cell carcinoma (LSCC) patients who underwent laryngectomy.

Methods: Retrospective review of 533 T2N0M0 glottic LSCC patients.

Results: Five-year cancer-specific survival (CSS) rate was 90.0%, and the overall survival (OS) rate was 89.1%. No statistically difference was found between the patients who have undergone total laryngectomy (5-year disease-free survival [DFS] = 80.7%, and the CSS = 86.7%) and those who have had partial laryngectomy (the 5-year DFS = 85.3%, and CSS = 91.1%). There was no difference in the CSS and DFS rates between patients with negative margins and those with positive margins following postoperative radiotherapy (PORT) ± chemotherapy (the CSS: 90.8% vs. 81.8%, $p = 0.458$ and 5-year DFS: 84.6% vs. 79.5%, $p = 0.371$). Patients who underwent vertical partial laryngectomy (VPL) had better survival (5-year OS was 91.9%, and the CSS was 92.8%) than those who underwent cricohyoidoepiglottopexy (CHEP) or cricohyoidopexy (CHP) (the 5-year OS = 83.8%, $p = 0.022$ and CSS = 84.9%, $p = 0.038$).

Conclusions: Surgery remains the gold standard for treating T2N0M0 glottic LSCC patients because it can achieve satisfactory oncological outcomes. Regarding the systemic conditions, the effect of partial laryngectomy is similar to that of total laryngectomy. Moreover, partial laryngectomy preserves the function of the larynx. VPL may be superior to CHP/CHEP, depending upon the invasiveness of the tumor.

KEYWORDS

LSCC, oncological outcomes, T2N0M0

Jian Zhou and Cheng-Zhi Xu contributed equally to this study.

INTRODUCTION

Laryngeal carcinoma is one of the most commonly discovered head and neck tumors.[1] Forty percent of the patients detected the cancer in the early phase, generally owing to seeking treatment for sore throat.[2,3] Around two-thirds of laryngeal malignancies occurred in the glottic area, and 80%–85% of these patients present with early-stage (T1–T2) malignancy.[4]

According to the National Comprehensive Cancer Network guidelines, patients of stage I (T1N0M0) and stage II (T2N0M0) ought to be cured with definitive radiation therapy (RT) or surgery.[5]

Conventional treatments for T2N0M0 glottic cancer include traditional surgical procedures to partially or totally remove the larynx and RT. The treatment choice is based on the physician's experience, hospital policy, and patient willingness.

Regular RT gives rise to high cure rates for T1 and T2 glottic malignancies. Nevertheless, patients who underwent RT may experience acute side effects such as laryngeal edema, sore throat, radiation dermatitis, and late side effects like an increased risk of stroke and carotid artery stenosis.[6,7] Generally speaking, nonsurgical treatment has a higher throat protection rate and sound quality, but long-term side effects also have adverse effects on the survival and quality of life of patients. Radical radiotherapy also often requires higher treatment costs and longer treatment time in China than open surgery. Therefore, many patients with early laryngeal cancer tend to choose surgery as the first choice of treatment.[8]

For cancers arising from the glottis location, the 5-year cancer-specific survival (CSS) rate of stage I tumor was reported to be 94%–99%, with an outstanding laryngeal preservation rate of about 95%. But, both the rates were reduced drastically for stage II glottic cancers, with the 5-year CSS rate of 79%–95% and laryngeal preservation rate of 76%–82%.[9–11] Due to the detection of worse outcomes in T2 cancers, the conventional approach of giving the same treatment to patients with these two stages of cancer has been challenged.[12,13] Several studies have also reported the survival advantage in early-stage LSCC patients who underwent surgery.[14–16]

The research aimed to study the oncological consequences of T2N0M0 glottic LSCC patients treated with the surgical approach. A total of 533 glottic LSCC patient records diagnosed with T2N0M0 were retrospectively reviewed. The medical parameters and demographics were assessed through a 10-year follow-up after the operation.

METHODS

Patients and preoperative processes

This research was permitted by the Ethics Committee of the Eye, Ear, Nose, and Throat Hospital at Fudan University. 533 T2N0M0 glottic LSCC patients in the Eye, Ear, Nose, and Throat Hospital of Fudan University from January 2005 to December 2010 were recruited. The participants underwent surgical management. All procedures were in accordance with the ethical standards of the committee on human experimentation of the institution or the Helsinki Declaration of 1975 as revised in 1983. The clinical information, including sex, age, alcohol consumption, cigarette smoking, surgical management, medical history, neck dissection, margin status, and postoperative treatment, were documented (Tables 1–3). None of the patients had preoperative chemotherapy or RT. All the patients were treated with primary surgery with or without adjuvant treatment. The diagnosis of LSCC was made based on the pathology report on both the primary cancer biopsies and postoperative specimens. Medical follow-up of the patients was done by the doctors at our hospital. All patients were followed up. Following were the inclusion criteria: (1) patients who received primary surgery in our center and (2) patients who had resectable LSCC and underwent surgery to cure it by removing the entire tumor.

TABLE 1 Demographics and clinical characteristics of T2N0M0 glottic laryngeal squamous cell carcinoma patients.

Characteristics	No. of patients	%	*HR (95%CI)* of DFS	*p* value
Age (categories)				
<60	275	51.6	1	0.140
≥60	258	48.4	1.288 (0.920–1.803)	
Sex			-	-
Male	525	98.5		
Female	8	1.5		
Smoking status				
Smoking	395	74.1	1	0.896
No smoking	138	25.9	0.974 (0.663–1.433)	
Drinking status				
Drinking	278	52.2	1	0.513
No drinking	255	47.8	1.119 (0.799–1.567)	
Past history			-	-
Hypertension	75	14.1		
Diabetes	15	2.8		
Hypertension and diabetes	7	1.3		
No past history	436	81.8		
Precancerous lesion			-	-
Leukoplakia	28	5.3		
Amyloidosis	1	0.2		
No precancerous lesion	504	94.5		

Abbreviations: -, means no data; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio.

TABLE 2 Multivariable regression analysis of demographics and clinical characteristics.

Characteristics	*p* value	Exp(B)	*CI* of 95.0% Exp(B)
Age	0.071	0.708	0.487–1.031
Sex	0.954	0.958	0.224–4.088
Smoking status	0.262	1.330	0.808–2.187
Drinking status	0.281	0.794	0.521–1.208
Past history	0.281	0.822	0.575–1.174
Precancerous lesion	0.734	1.112	0.602–2.057
Treatments	0.203	0.771	0.517–1.150

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 3 Summary of the surgical treatments given to T2N0M0 glottic LSCC patients.

Characteristics	No. of patients	%
Treatments		
Total laryngectomy	133	25.0
Partial laryngectomy	400	75.0
VPL	310	77.5
CHEP/CHP	90	22.5
Neck dissection		
Unilateral neck dissection	14	2.6
Bilateral neck dissection	4	0.8
Surgical margin		
Negative	489	91.7
Positive rescue therapy	44	8.3
Treatments		
Surgical treatment	484	90.8
Surgery and PORT ± chemotherapy	49	9.2

Abbreviations: CHEP, cricohyoidoepiglottopexy; CHP, cricohyoidopexy; LSCC, laryngeal squamous cell carcinoma; PORT, postoperative radiotherapy; VPL, vertical partial laryngectomy.

Exclusion criteria were the following: patients who received preoperative RT ± chemotherapy.

Surgical strategies

All patients underwent either partial laryngectomy (including vertical partial laryngectomy [VPL], cricohyoidoepiglottopexy [CHEP]/cricohyoidopexy [CHP]) or total laryngectomy based on preoperative assessments of malignancy. Neck dissection was performed on 18 patients (Table 3). Patients were diagnosed with squamous cell carcinoma postoperatively via histopathological examination. Most of the patients underwent VPL, CHEP, or CHP. Patients who had significant cardiopulmonary comorbidities or were at high risk of aspiration underwent total laryngectomy. The patients with positive surgical margins and close margin were administered with postoperative radiotherapy (PORT) ± chemotherapy. The specific scheme was described in the previous report.[17]

Postoperative processes

All patients were encouraged to start the swallowing rehabilitation in the early period after the operation. The feeding tube was removed when the patients' oral intake had been improved. Tracheostomy decannulation was taken place following the preservation of regular breathing without dyspnea for at least 48 h. The postoperative complications were detailed, and the related salvage managements were undertook to these ones. Regional, local, and local-regional recurrence, as well as distant metastasis, were confirmed. The related salvage management (including total laryngectomy, neck dissection, radiotherapy ± chemotherapy) for these ones were also detailed.

Statistical evaluates

Statistical evaluates were performed using SPSS version 20.0. Follow-up time was documented from the operation day to the date of the latest communication or death. Life table analysis was used to analyze the disease-free survival (DFS), CSS, and overall survival (OS) rates at 5 and 10 years. The Kaplan–Meier analyses were used to calculate the CSS rate, DFS rate, and OS rate among the diverse collections, while the log-rank assessment was applied to regulate the significance of the detected differences. The hazard ratio and 95% confidence interval of the predictive features were considered. $p < 0.05$ was considered statistically significant.

RESULTS

Medical characteristics and demographics

This research included 533 T2N0M0 glottic LSCC patients who underwent laryngectomy. The median observation time of this research was 96.7 ± 38.6 months (range: 7.5–138.6 months). The mean hospitalization time was 22.60 ± 6.2 days, ranging from 2 to 51 days. The average nasogastric feeding tube removal period was 11.39 ± 4.6 days, ranging from 0 to 46 days. The demographics and medical characteristics are described in Table 1. This research involved eight females (1.5%) and 525 males (98.5%), with a mean age of 60.2 ± 9.3 years (range: 35–89 years). Among the patients, 395 (74.1%) had smoking habits, and 278 (52.2%) had drinking habits in the past.

The surgical management of laryngeal cancer included total laryngectomy (133, 25.0%) and partial laryngectomy (400, 75.0%),

such as VPL (310, 77.5%), CHEP/CHP (90, 22.5%), and neck dissection were recorded (Table 3).

CSS and DFS outcomes

In this research, the 5-year DFS of 533 T2N0M0 glottic LSCC patients was 84.1% (Table 4, Figure 1). Of 49 (9.2%) LSCC recurrences, 20 were local, 25 were locoregional, and four were distant metastasis. The 5-year CSS was 90.0%, and the OS was 89.1% (Table 4, Figure 1).

For T2N0M0 glottic LSCC patients who underwent total laryngectomy, the 5-year DFS was 80.7%, and the 5-year CSS was 86.7%. For T2N0M0 glottic LSCC patients who underwent partial laryngectomy, the 5-year DFS was 85.3% ($p = 0.249$), and the 5-year CSS was 91.1% ($p = 0.181$) (Tables 4 and 5, Figure 2).

This research showed the association between DFS, CSS, and surgical margin status of T2N0M0 glottic LSCC patients. Patients with positive surgical margins underwent PORT; some also underwent chemotherapy. No statistically significant difference was discovered in the 5-year CSS and DFS between T2N0M0 glottic LSCC patients with negative margins and those with positive margins following PORT (DFS: 84.6% vs. 79.5%, $p = 0.371$; CSS: 90.8% vs. 81.8%, $p = 0.458$, Figure 3).

Finally, this study compared the effects of different surgical approaches of partial laryngectomy (VPL vs. CHP/CHEP) on the survival of T2N0M0 glottic LSCC patients. The outcome presented that the 5-year OS and CSS of patients who underwent VPL were higher than those who underwent CHP/CHEP (OS: 91.9% vs. 83.8%, $p = 0.022$; CSS: 92.8% vs. 84.9%, $p = 0.038$, Figure 4, Tables 4 and 5).

TABLE 4 The OS, DFS and CSS rates of T2N0M0 glottic LSCC patients distributed among different groups(%).

Characteristics	5 years			10 years		
	OS	CSS	DFS	OS	CSS	DFS
All of the patients	89.1	90.0	84.1	76.8	78.7	74.3
Surgical approach						
TL	86.0	86.7	80.7	70.8	74.8	70.8
PL	90.1	91.1	85.3	78.9	80.0	75.4
Surgical margin						
Negative	89.8	90.8	84.6	77.4	79.5	75.3
Positive with rescue therapy	81.8	81.8	79.5	72.7	72.7	66.4
Larynx-preservation approach						
VPL	91.9	92.8	86.4	81.1	81.9	76.0
CHP/CHEP	83.8	84.9	78.1	70.8	72.9	69.0

Abbreviations: CHEP, cricohyoidoepiglottopexy; CHP, cricohyoidopexy; CSS, cancer-specific survival; DFS, disease-free survival; LSCC, laryngeal squamous cell carcinoma; OS, overall survival; PL, partial laryngectomy; TL, total laryngectomy; VPL, vertical partial laryngectomy.

DISCUSSION

LSCC is a unique carcinoma in which the survival has deteriorated in the last 20 years. Though nonsurgical treatment has higher laryngeal preservation rate and voice quality, but long-term toxic and side effects also have adverse effects on patients' survival and quality of life. So, one of the reasons could be the increased use of nonsurgical primary treatment.[18,19]

The therapy results of the T2N0M0 laryngeal tumor are inferior to that of the T1N0M0, despite the same initial phase being considered.[20,21] Previous research of conventional RT have described the 5-year local control rates of 84%–95% for T1a and 50%–85% for T2 glottic tumors.[14,22,23] T2N0M0 patients have a 25%-50% recurrence rate, which is two times higher than that of T1N0M0 patients, owing to local failure in the laryngeal tumor. Unsatisfactory results have been reported in the OS, DSS, and laryngeal-preserving survival rates in T2N0M0 laryngeal tumor.[24,25]

One possible explanation for poorer outcomes in patients with T2 laryngeal cancers is the nodus in differentiating between T2 and T3 cancers, leading to understaging and eventually undertreatment.

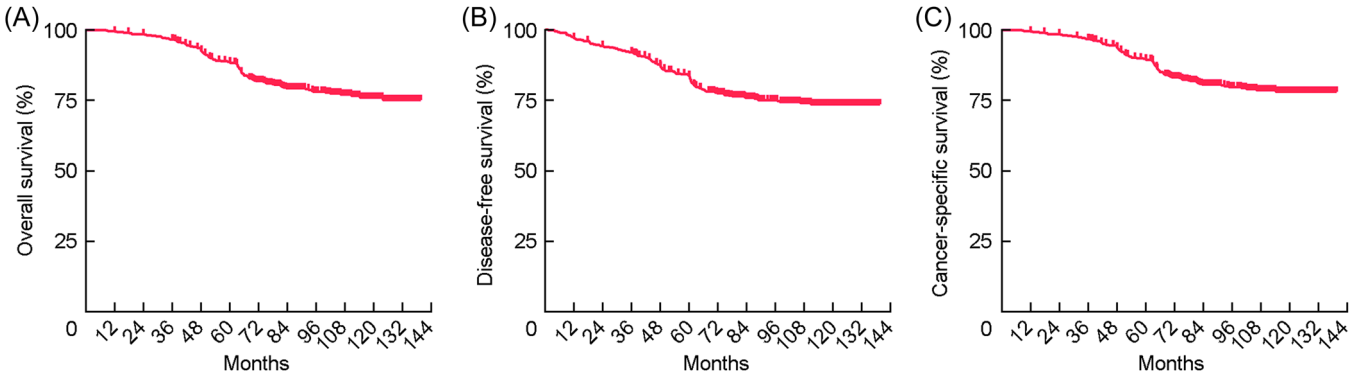

FIGURE 1 Total Kaplan–Meier overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS) curves; (A) total OS curves of 533 T2N0M0 glottic laryngeal squamous cell carcinoma(LSCC) patients; (B) total DFS curves of T2N0M0 glottic LSCC patients; (C) total CSS curves of T2N0M0 glottic LSCC patients.

TABLE 5 Multivariate Cox proportional hazards regression of DFS and CSS in T2N0M0 glottic LSCC patients.

Characteristics	DFS *HR* (95% *CI*)	*p* value	CSS *HR* (95% *CI*)	*p* value
Operation method				
TL	1.000	0.249	1.000	0.181
PL	0.797 (0.530–1.198)		0.748 (0.473–1.181)	
Surgical margin				
Negative	1.000	0.371	1.000	0.458
Positive with rescue therapy	1.299 (0.686–2.459)		1.280 (0.621–2.637)	
Partial laryngectomy method				
VPL	1.000	0.148	1.000	0.038
CHP/CHEP	1.400 (0.878–2.387)		1.705 (1.034–3.330)	

Note: Bold values represent that *p* were two-sided and $p < 0.05$ was statistically significant.

Abbreviation: CHEP, cricohyoidoepiglottopexy; CHP, cricohyoidopexy; CI, confidence interval; CSS, cancer-specific disease; DFS, disease-free survival; HR, hazard ratio; LSCC, laryngeal squamous cell carcinoma; PL, partial laryngectomy; TL, total laryngectomy; VPL, vertical partial laryngectomy.

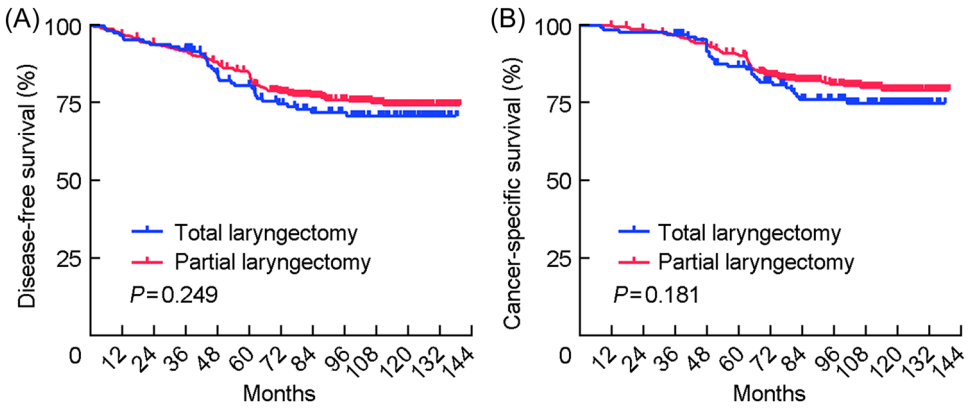

FIGURE 2 Kaplan–Meier disease-free survival (DFS) and cancer-specific survival (CSS) curves stratified according to partial and total laryngectomy. (A) DFS curves stratified by types of laryngectomy; (B) CSS curves stratified based on surgical procedures.

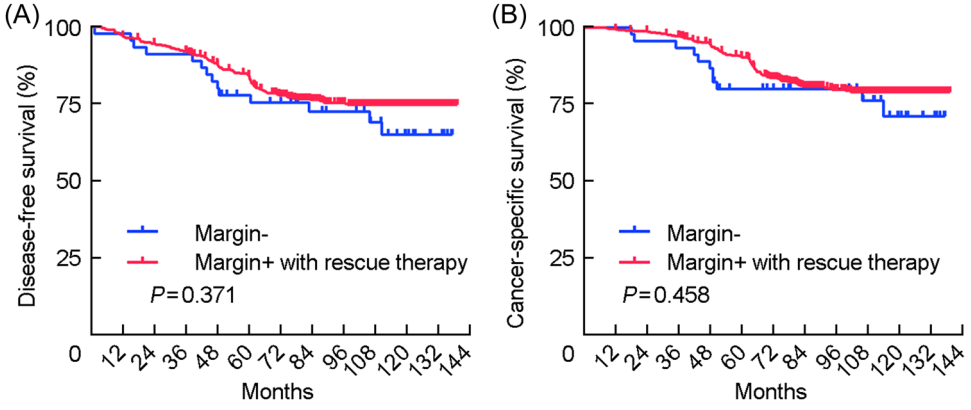

FIGURE 3 Kaplan–Meier disease-free survival (DFS) and cancer-specific survival (CSS) curves stratified by negative and positive surgical margin following the rescue treatment. (A) DFS curves stratified according to margin status; (B) CSS curves stratified according to margin status.

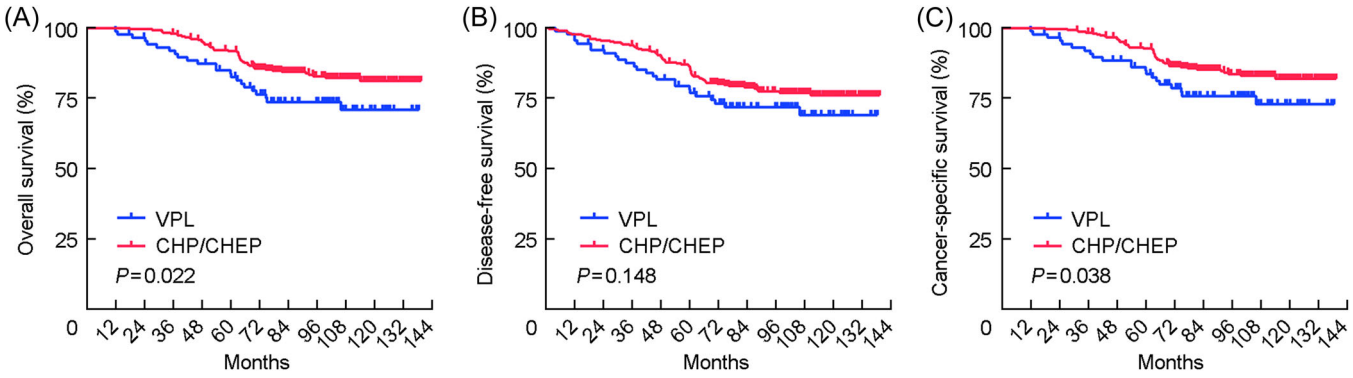

FIGURE 4 Kaplan–Meier overall survival (OS), disease-free survival (DFS), and cancer-specific survival (CSS) curves stratified by different types of partial laryngectomy (vertical partial laryngectomy [VPL] vs. cricohyoidopexy [CHP]/cricohyoidoepiglottopexy [CHEP]). (A) OS curves stratified according to the partial laryngectomy approaches; (B) DFS curves stratified according to the partial laryngectomy approaches; (C) CSS curves stratified according to the partial laryngectomy approaches.

This is particularly true with respect to the difficulty in defining thyroid cartilage and/or paraglottic space invasion on cross-sectional imaging in the early to middle phase of laryngeal cancers.[26] The staging difference is relatively easy to identify in surgical patients but more difficult to distinguish in nonsurgical patients.

The demand to preserve laryngeal function further confuses the choice of management approaches for laryngeal tumor. Furthermore, many issues such as lung function, tumor extent, lifestyle necessities, occupations, and psychological sustenance have to be considered while determining treatment options for individuals with laryngeal tumors.[27]

This study showed that the oncological outcomes of 533 surgically treated patients, with 84.1% of 5-year DFS and 90.0% of CSS (Figure 1), were inspiring. The operating management given to the patients involved in this study included total laryngectomy (133, 25.0%) and partial laryngectomy (400, 75.0%). For T2N0M0 glottic LSCC patients who had total laryngectomy, the 5-year DFS rate was 80.7%, and the 5-year CSS rate was 86.7%. For T2N0M0 glottic LSCC ones who received partial laryngectomy, the 5-year DFS was 85.3% ($p = 0.249$), and the 5-year CSS was 91.1% ($p = 0.181$) (Tables 4 and 5, Figure 2). So, some T2N0M0 glottic LSCC patients could achieve satisfactory oncological and functional outcomes from partial laryngectomy techniques, including VPL, CHP, and CHEP. The survival rates for patients who had the surgery are higher than those who had radiotherapy in previously published reports,[9–11] which may be related to the higher local control rate and sparing long-term toxicity from radiotherapy.

Many studies have shown that radical radiotherapy is comparable to open surgery in early laryngeal cancer. In other words, there is no statistical difference in survival. However, most retrospective cohort studies have reported higher 5-year survival and local control rates in the open surgery group than in the radiotherapy group.[28,29] Megwalu and Panossian conducted a statistical reanalysis of 5301 patients in the Surveillance, Epidemiology, and End Results database from 1992 to 2009. It was found that the patients with early laryngeal tumor who underwent operation had better survival benefits than the nonsurgical group.[30] Although RT can give a better voice to a greater extent than open surgery, it is often more expensive.[31,32] Survival is always a priority when selecting treatment modalities. Our results suggest that patients with T2N0M0 can achieve an OS rate of 89.1% at 5 years, which gives us more confidence to choose surgical treatment for suitable patients.

Positive margins often affect the local control rate and prognosis of patients with laryngeal tumor.[33] For patients with positive margins, reresection and PORT ± chemotherapy can be used to improve survival benefits. Since reoperation often reduces the laryngeal function, and it is difficult to identify a clear, safe margin, PORT was mainly adopted as a rescue strategy. In our study, the PORT was given to patients whose surgical margins were positive. No statistical difference was observed in the 5-year CSS and DFS between T2N0M0 glottic LSCC patients whose margin was negative and those whose margin was positive following the rescue therapy (DFS: 84.6% vs. 79.5%, $p = 0.371$; CSS: 90.8% vs. 81.8%, $p = 0.458$, Figure 3). Consequently, we recommend that PORT ± chemotherapy is effective management for T2N0M0 glottic laryngeal cancer patients with positive margins. However, it should be aware that PORT increases patients' toxicity and economic burden, and the survival rates are lower than that of patients with a negative margin. Therefore, on the premise of preserving laryngeal function, to assess the margin intraoperatively by frozen section with accurate orientation of the specimen by the surgeons and attaining negative margins on the table would be more ideal in these suitcases.

To preserve the larynx function with partial laryngectomy, VPL, CHEP, and CHP are the common surgical approaches. Generally, CHEP/CHP is used for larger tumors due to its high extubation success rate and simplicity in our hospital. In this study, our outcome presented that the 5-year OS and CSS rates of patients with VPL were better than those with CHP/CHEP (OS: 91.9% vs. 83.8%, $p = 0.022$; CSS: 92.8% vs. 84.9%, $p = 0.038$, Figure 4, Tables 4 and 5). This may be due to a larger tumor area or deeper invasion. One of the possible reasons for worse survival outcomes in CHP/CHEP vs VPL be understaging of these tumors. Therefore, for patients with T2N0M0, our data suggest that VPL can be a better choice for open surgery when the depth of tumor invasion is “shallow.”

Nevertheless, several limitations exist in the present study. This research was a single-center retrospective work, resulting in selection bias. There is also a lack of systematic voice and swallowing function assessment for patients undergoing partial laryngectomy, especially for VPL and CHEP/CHP, the two main laryngopharyngeal sparing procedures. Based on our clinical observations, VPL was shown to be having a better articulation quality, faster recovery of swallowing function, and lower aspiration rate. However, there is still a lack of systematic and comprehensive scale evaluation and an objective measurement basis, which needs further study.

Taken together, surgical treatment for T2N0M0 laryngeal squamous cell carcinoma patients can obtain satisfactory oncological outcome, and avoid the long-term toxicity of RT and CRT. PORT ± chemotherapy is an effective rescue therapy for T2N0M0 glottic LSCC patients with positive surgical margins. Furthermore, VPL offers better survival outcomes than CHEP/CHP if the extent of tumor invasion allows.

AUTHOR CONTRIBUTION

All authors participated in the design and coordination of the study, and read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Professor Liang Zhou is a member of World Journal of Otorhinolaryngology–Head & Neck Surgery (WJOHNS) editorial board and is not involved in the peer review process of this article.

DATA AVAILABILITY STATEMENT

The authors have nothing to report.

ETHICS STATEMENT

This research was permitted by the Ethics Committee of the Eye, Ear, Nose, and Throat Hospital at Fudan University (approval no. 2021039).

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