Survival outcomes in patients with T3-4aN0M0 glottic laryngeal squamous cell carcinoma and evaluation of postoperative radiotherapy

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Received June 23, 2022; Accepted September 30, 2022

DOI: 10.3892/ol.2022.13554

Abstract. This study aimed to evaluate the clinical outcomes of patients with T3-4aN0M0 glottic laryngeal squamous cell carcinoma (LSCC) treated with laryngectomy, and to assess the postoperative radiotherapy (PORT) results in terms of the survival of T3-T4aN0M0 patients with negative margins. This was a retrospective review of 369 T3-4aN0M0 glottic LSCC cases. The 5-year cancer-specific survival (CSS) and overall survival (OS) rates were 67.5 and 66.7%, respectively. Patients who received total laryngectomy had worse survival [5-year CSS, 62.5%; disease-free survival (DFS), 56.2%] than those who underwent partial laryngectomy (5-year CSS, 79.3%; DFS, 65.4%). More advanced-stage cancer is a predictor of poor survival. There was no significant difference in CSS or DFS between patients with positive margins following rescue therapy and those with negative margins. Furthermore, no difference in the survival rates was observed between patients with negative margins who received PORT and those who did not (5-year DFS: 59.1 vs. 63.8%, P=0.057 and CSS: 62.5 vs. 69.5%, P=0.074). For T3-4aN0M0 glottic LSCC patients, surgical treatment remained a good option, as it can achieve satisfactory oncological outcomes. However, PORT did not increase survival in surgically managed pT3-4aN0M0 LSCC patients with negative margins.

Introduction

Laryngeal carcinoma is a common type of airway cancer, and squamous cell carcinoma is the pathological type most often observed in the respiratory system (1). Although laryngeal tumors represent only 2-5% of all carcinomas, they are of significant interest as the larynx plays a vital role in swallowing and speaking. Additionally, laryngeal tumors can also severely affect a patient's quality of life. Currently, conventional management of LSCC consists of radiotherapy (RT), chemoradiotherapy (CRT), and surgery.

The incidence and mortality rates of laryngeal cancer are 1.86/100,000 and 1.01/100,000, respectively, ranking 21st most common cause of cancer-associated death among all cancer types in China (2).

The value of postoperative adjuvant therapy for locally advanced cancer with lymph node-negative status (N0) remains unclear (3). Furthermore, it is yet to be determined what the best adjuvant treatment is for locally advanced N0 cancer in patients who have undergone primary surgical treatment (4-7). While RT is used to preserve laryngeal function, it may also lead to adverse effects following laryngeal surgery, such as xerostomia, fibrosis, laryngeal edema, tissue necrosis, and dysphagia, and eventually reduce a patient's quality of life. Therefore, the value of adjuvant therapies should be balanced against any possible complications, and thus patients should be fully informed before making a decision (7).

The National Comprehensive Cancer Network guiding principle (version 02.2020) recommends PORT for patients with pT4N0 tumors, positive or close margins, and destructive pathological features. In contrast, for patients with pT3 tumors, adjuvant management is elective (8).

Some retrospective studies reported that laryngeal preservation with CRT, rather than removing the larynx entirely, for locally advanced cancer resulted in reduced survival rates among laryngeal carcinoma (LC) patients (9-11).

Whether PORT is beneficial in T3-4a N0M0 laryngeal cancer patients remains contested. Given the doubt surrounding suitable adjuvant treatments for T3N0 and T4aN0 LSCC, this study aimed to determine the oncological results of T3-4a N0M0 glottic LSCC treated with the operating method and to determine whether PORT is related to increased survival rates in surgically managed T3-4aN0M0 LSCC patients with negative margins.

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Key words: laryngeal squamous cell carcinoma, T3-4aN0M0, survival outcomes, surgery, postoperative radiotherapy

Materials and methods

Patients and preoperative procedures. This study was approved by the Ethics Committee of the Eye, Ear, Nose, and Throat Hospital at Fudan University (approval no. 2021039). The study was conducted following the ethical standards of The Committee on Human Experimentation of the Eye, Ear, Nose and Throat Hospital at Fudan University as well as that described in the Declaration of Helsinki of 1975 as revised in 1983 (12). All patients provided informed written consent to participate in this study. A total of 369 patients diagnosed with T3-4aN0M0 glottis LSCC between January 2005 and December 2010 were included. Overall, 357 (96.7%) patients were men and 12 (3.3%) patients were women. The mean age was 60.8±10.9 years (range, 30-85 years; median age, 60 years). The sex, smoking status, age, alcohol consumption, clinical and tumor, node, and metastasis (TNM) stage are shown in Table I. This study also recorded post-surgery information on PORT, surgical margins, and recurrence. When LSCC was diagnosed, the different treatment options were discussed with these patients and their families to assist them in determining the optimal treatment plan for them. Cancer staging was based on the TNM grouping criteria for LSCC staging designated by the Union for International Cancer Control (UICC) (13).

Operational procedures. The T3-4aN0M0 LSCC patients underwent either partial or total laryngectomy based on the assessment of malignancy, and the operations were performed as described previously (14). We defined margins <5 mm as close margins, which is still considered as negative margins, but PORT was routinely recommended in these cases (15). All patients were confirmed to have LSCC based on their postoperative pathological reports. The inclusion criteria were: i) Patients who received primary surgery, including total laryngectomy and partial laryngectomy, in the Eye, Ear, Nose and Throat Hospital; ii) patients diagnosed with LSCC pathologically; and iii) patients who had resectable LSCC and had an operation with the purpose of curing the cancer. The exclusion criteria were: i) Patients treated with only primary RT or CRT and ii) patients treated with neoadjuvant chemotherapy.

Postoperative procedures. The postoperative procedures were performed as described previously (14). When the postoperative margins were positive, we recommend that the patient undergo rescue therapy, including postoperative supplemental RT and CRT. According to the physician's opinion (for these patients, we routinely recommend postoperative radiotherapy) and the patient's conditions, certain patients with negative surgical margins also underwent PORT. A total of 54 patients with positive margins received adjuvant chemotherapy in addition to PORT. Complementary RT or CRT was generally started within 4-6 weeks after surgery. RT and chemotherapy were performed as described previously (16). The curative irradiation dose was 60-74 Gy (1.8-2.0 Gy/fraction) from weeks 6-7. Radiation fields covered both the primary tumor location and the involved lymph nodes. Platinum-based concurrent CRT was performed based on one of three regimens: i) cisplatin (DDP) regimen-DDP (45-50 mg/m^2/day) on days 1-3; ii) DDP combined with 5-fluorouracil (5-FU) (PF regimen)-DDP (40 mg/m^2/day) on days 1-3 and 5-FU (750-800 mg/m^2/day) on days 1-4; or iii) carboplatin (CBP)-based regimen-CBP, calcium folinate, and tegafur (200, 300, or 1,000 mg/m^2/day, respectively) on days 1-3 for 1-2 cycles.

Follow-up. Follow-up time was documented from the day of operation until the day of the last contact or death. The follow-up methods primarily included outpatient regular follow-up, telephone consultation, and email consultation. The standard of local control is based on the results of electronic laryngoscopy and CT/MRI examination, with no new recurrence of the larynx and cervical lymph nodes.

Statistical analyses. The demographics and clinical features are described as frequencies and proportions. Statistical analysis was performed using SPSS version 19.0 (IBM Corp.). Follow-up time was documented from the day of operation until the day of the latest encounter or death. Life table examination was conducted to determine the DFS, CSS, and OS rates after 5 and 10 years. Kaplan-Meier analysis was used to assess the CSS, DFS, and OS rates among the different groups, and a log-rank test was used to compare survival. The 95% confidence interval (CI) and hazard ratio associated with the prognostic agents were also assessed. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics and demographics. This study included 369 T3-4aN0M0 glottic LSCC patients who underwent laryngectomy. The mean ± SD follow-up time was 95.3±39.8 months (range, 6.6-139.4 months), and the median period of follow-up was 89 months. The average hospitalization phase was 25.89±8.7 days, with a range of 11-98 days. The mean ± SD nasogastric feeding tube removal period was 13.54±11.18 days, ranging from 4-192 days. The clinical demographics and characteristics are described in Table I. Of the patients, 255 (69.1%) were smokers, and 162 (43.9%) consumed alcohol. A total of 282 (76.4%) patients had stage III tumor, and 87 (23.6%) had a stage IV tumor. Among them, 315 (85.4%) patients had negative surgical margins. Of the patients with negative margins, 57 (18.1%) underwent PORT.

Surgery that involved total laryngectomy (261, 70.7%), partial laryngectomy (108, 29.3%), including vertical partial laryngectomy (VPL) (64, 59.3%), cricohyoidoepiglottopexy (CHEP) (41, 38.0%), cricohyoidopexy (CHP) (2, 1.9%), CO_2 laser surgery (1, 0.9%), and Turker (1, 0.9%), as well as neck lymph node dissection are documented in Table II.

DFS and CSS results. The 5-year DFS of the 369 T3-4aN0M0 glottic LSCC patients was 59.3% (Table III, Fig. 1). The 5-year CSS was 67.5%, and the OS was 66.7% (Table III, Fig. 1).

For T3-4aN0M0 glottic patients who underwent total laryngectomy, the 5-year DFS rate was 56.2%, and the 5-year CSS rate was 62.5%. Conversely, the 5-year DFS and CSS rates for patients who underwent partial laryngectomy were 65.4% (P=0.048) and 79.3% (P=0.003), respectively, which were both higher than that in the patients who underwent total laryngectomy (Fig. 2, Tables III and IV).

To assess the relationship between DFS, CSS, and T3-4aN0M0 glottic LSCC tumor stage, log-rank tests were

Table I. Clinical characteristics of the patients.

Factor	Value	%	5 years CSS, %	P-value[c]
Age, years				
Mean	60.8±10.9	-	-	
Range	30-85	-	-	
Age, n				
<60	180	48.8	71.1	0.042[a]
≥60	189	51.2	64.0	
Sex, n				
Male	357	97.3	66.6	0.060
Female	12	2.7	91.7	
Smoking status, n				
Smoking	255	69.1	68.2	0.430
No smoking	114	30.9	65.8	
Drinking status, n				
Drinking	162	43.9	66.5	0.961
No Drinking	207	56.1	68.2	
Margin situation, n				
Negative	315	85.4	67.7	0.920
Positive with rescue therapy	54	14.6	66.1	
PORT with negative margins, n				
Yes	57	18.1	62.5	0.074
No	258	81.9	69.5	
Clinical stage, n				
III (T3)	282	76.4	73.6	<0.001[b]
IV (T4a)	87	23.6	47.4	

[a]P<0.05; [b]P<0.001; [c]P-values were calculated using a log-rank test for comparison of survival curves of the 5-year CSS percentage.

Table II. Summary of the surgical treatments.

Treatment	n	%
Total laryngectomy	261	70.7
Partial laryngectomy	108	29.3
Vertical partial laryngectomy	64	59.3
Cricohyoidoepiglottopexy	41	38.0
Cricohyoidopexy	2	1.9
Turker	1	0.9
Neck dissection		
Unilateral radical neck dissection	19	5.1
Unilateral modified neck dissection	4	1.1
Unilateral selective neck dissection	10	2.7
One side radical neck dissection, one side selective neck dissection	1	0.3
Bilateral neck dissection		
Bilateral modified neck dissection	1	0.3
Bilateral selective neck dissection	1	0.3

used. The 5-year DFS and CSS rates of patients with stage III tumors were higher than those of patients with stage IV tumors (DFS, 63.4 vs. 44.5%, P<0.01; CSS, 73.6 vs. 47.4%, P<0.01; Fig. 3, Tables III and IV).

This study also investigated the relationship between the DFS, CSS, and surgical margin status of the T3-4a N0M0 glottic LSCC. The LSCC patients with positive surgical margins or close margins underwent PORT, and certain patients were also treated with chemotherapy. No significant difference was detected in the 5-year CSS and DFS rates between T3-4a N0M0 glottic patients with negative margins and those with positive margins following rescue therapy (DFS, 59.0 vs. 61.0%, P=0.732; CSS, 67.7 vs. 66.1%, P=0.920; Fig. 4).

Finally, the relationships between the CSS, DFS, and PORT status of T3-4aN0M0 glottic patients with negative margins were assessed. No significant difference was detected in the CSS and DFS rates between the patients with negative margins who underwent PORT compared with those who did not (57 cases vs. 258 cases; DFS, 59.1 vs. 63.8%, P=0.057; CSS, 62.5 vs. 69.5%, P=0.074; Tables III and IV, Fig. 5). However, T3-4aN0M0 glottic patients with negative margins who did not receive PORT tended to have a better survival rate than those who received PORT. This trend was especially evident in the 10-year survival rate (DFS, 41.9 vs. 60.6%; CSS, 49.4 vs. 64.7%; Tables III and IV). To avoid the clinical staging from interfering with this result, we studied the effect of the PORT status of LSCC with negative margins in T3 and T4a patients

Table III. OS, DFS and CSS rates of T3-4aN0M0 glottic LSCC patients distributed among different groups.

	5 years			10 years		
Factor	OS %	CSS %	DFS %	OS %	CSS %	DFS %
T3,4aN0M0 glottic LSCC with laryngectomy	66.7	67.5	59.3	58	60.3	54
Operation method						
Total laryngectomy	61.7	62.5	56.2	51.7	54.7	50
Partial laryngectomy	78.5	79.3	65.4	72.9	73.6	63.4
Clinical stage						
Stage III	72.9	73.6	63.4	65.2	67	59.7
Stage IV	46.3	47.4	44.5	34.8	38.3	36.2
Margin status						
Negative	67.1	67.7	59	57.6	60.1	53.5
Positive with rescue therapy	64.6	66.1	61	60.7	62.1	57.1
PORT with negative margins						
No	68.7	69.5	63.8	61.6	64.7	60.6
Yes	62.5	62.5	59.1	49.4	49.4	41.9

LSCC, laryngeal squamous cell carcinoma; PORT, postoperative radiotherapy.

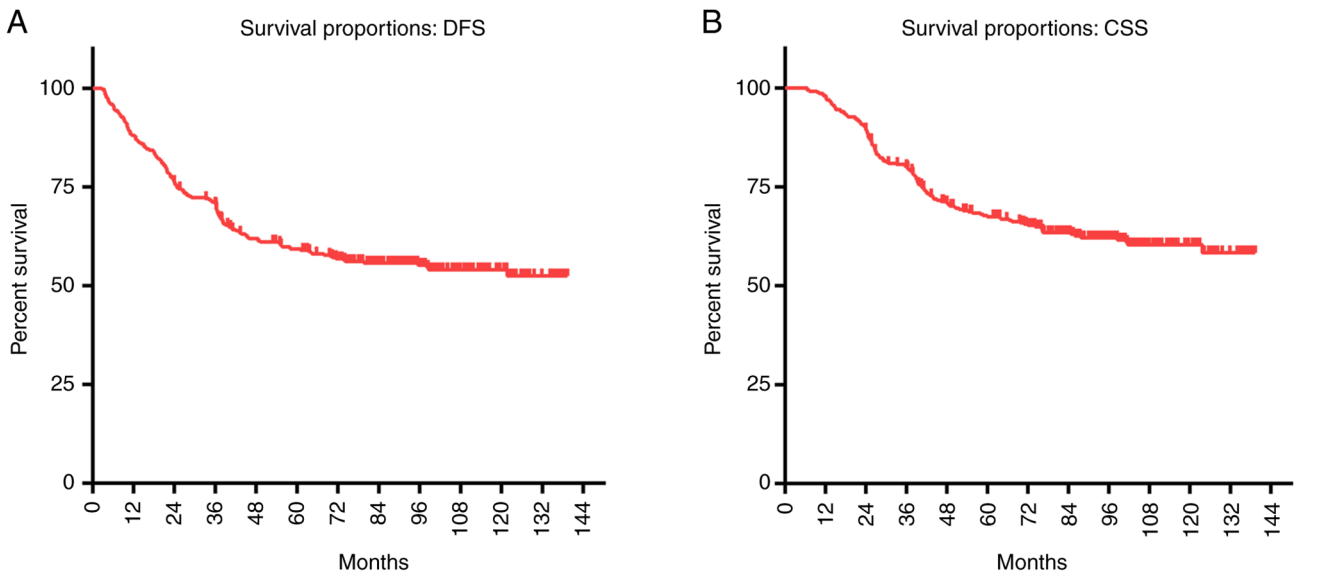

Figure 1. DFS and CSS curves. (A) DFS curve of the 369 T3-4aN0M0 glottic LSCC patients. (B) CSS curve of the 369 T3-4aN0M0 glottic LSCC patients. DFS, disease free survival; CSS, cancer-specific survival.

separately. Similar results were obtained (for T3 LSCC patients: DFS, P=0.068, CSS, P=0.529; for T4a LSCC patients: DFS, P=0.652, CSS, P=0.801; Tables III and IV, Fig. 5).

Discussion

LSCC is a unique carcinoma, the survival rates of which have worsened in the last 2 decades. Surprisingly, retrospective studies have reported reduced OS rates in patients with advanced laryngeal tumors even after the widespread adoption of RT-based laryngeal preservation methods (10,11,17-19). The guideline recommendations for the optimal management of locally advanced LC are focused on approaches that maximize laryngeal function without compromising the oncological results (20).

For LSCC patients treated with surgery, the ideal adjuvant treatment remains uncertain, especially for locally advanced lymph node-negative disease (21). To help answer this unresolved question, we assessed the survival outcomes of the current surgical approaches for T3-4a N0M0 glottic LSCC in China.

The results showed the oncological outcomes of 369 surgically treated patients, with a 66.7% 5-year OS rate, a 59.3% 5-year DFS rate, and a 67.5% CSS rate. The survival rate of

Table IV. Multivariate Cox proportional hazards regression analysis for DFS and CSS in patients with T3-4aN0M0 glottic LSCC.

Characteristics	DFS, HR (95% CI)	P-value	CSS, HR (95% CI)	P-value
Operation method				
Total laryngectomy	1.00	0.048[a]	1.000	0.003[a]
Partial laryngectomy	0.70 (0.51-1.00)		0.53 (0.40-0.83)	
Clinical stage				
Stage III	1.000	<0.001[c]	1.000	<0.001[b]
Stage IV	2.15 (1.74-3.80)		2.77 (2.48-5.92)	
Margin status				
Negative	1.00	0.732	1.00	0.920
Positive with rescue therapy	0.93 (0.60-1.43)		1.03 (0.64-1.65)	
Postoperative radiotherapy with negative margins				
No	1.00	0.057	1.00	0.074
Yes	1.64 (0.98-3.40)		1.64 (0.94-3.54)	

[a]P<0.05, [b]P<0.01, [c]P<0.001. DFS, disease-free survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval.

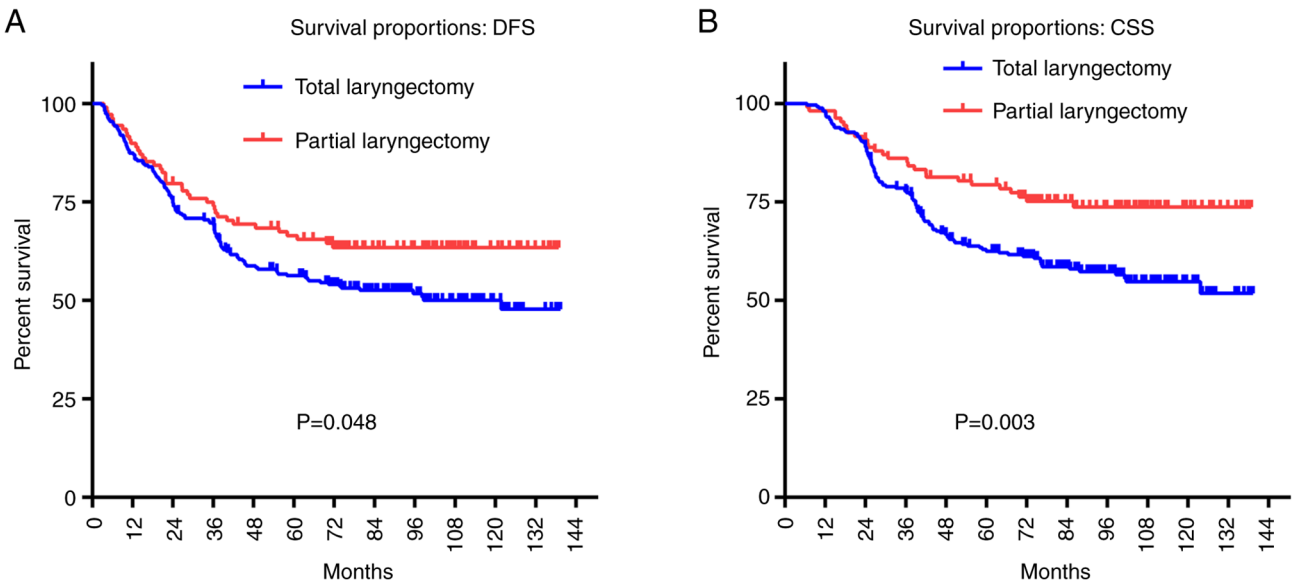

Figure 2. DFS and CSS curves stratified by the distribution of total laryngectomy and partial laryngectomy. (A) DFS and (B) CSS curves stratified based on method of operation. DFS, disease free survival; CSS, cancer-specific survival.

LSCC patients with partial laryngectomy was significantly higher than that of those with total laryngectomy for the following reasons: i) The vast majority of the patients who underwent partial laryngectomy had earlier stage tumors, with a higher proportion of T3 patients (97.2 vs. 67.8%, representing partial laryngectomy and total laryngectomy, respectively); ii) patients with total laryngectomy tended to be older and have more cardiopulmonary and other systemic comorbidities. Therefore, for patients with T3-4aN0M0 glottic LSCC, surgical laryngectomy techniques, including total laryngectomy, VPL, CHP, and CHEP, can achieve acceptable functional and oncological outcomes. Our findings are in agreement with previous reports that showed 5-year DFS and OS rates of 60-79 and 48-71%, respectively (4,14,22), following open laryngectomy.

Previous studies suggested that radical radiotherapy achieved higher laryngeal preservation rates with the same survival rate as surgery. However, the 5-year survival rate is only 53% (23), which is lower than the survival rate observed at our center. It is thus suggested that the treatment strategy for laryngeal cancer should be based on increasing the survival rate.

The results of the present study showed that patients with stage IV T3-4a N0M0 glottic LSCC had poorer CSS and DFS rates than stage III patients. No significant difference was detected in the CSS and DFS rates between patients whose margins were negative compared with those who were positive following PORT or CRT. Nguyen-Tan *et al* (24) discovered a strong relationship between T-stage LSCC and survival rates, with 5-year OS rates for pT4 and pT3 of 38 and 54%,

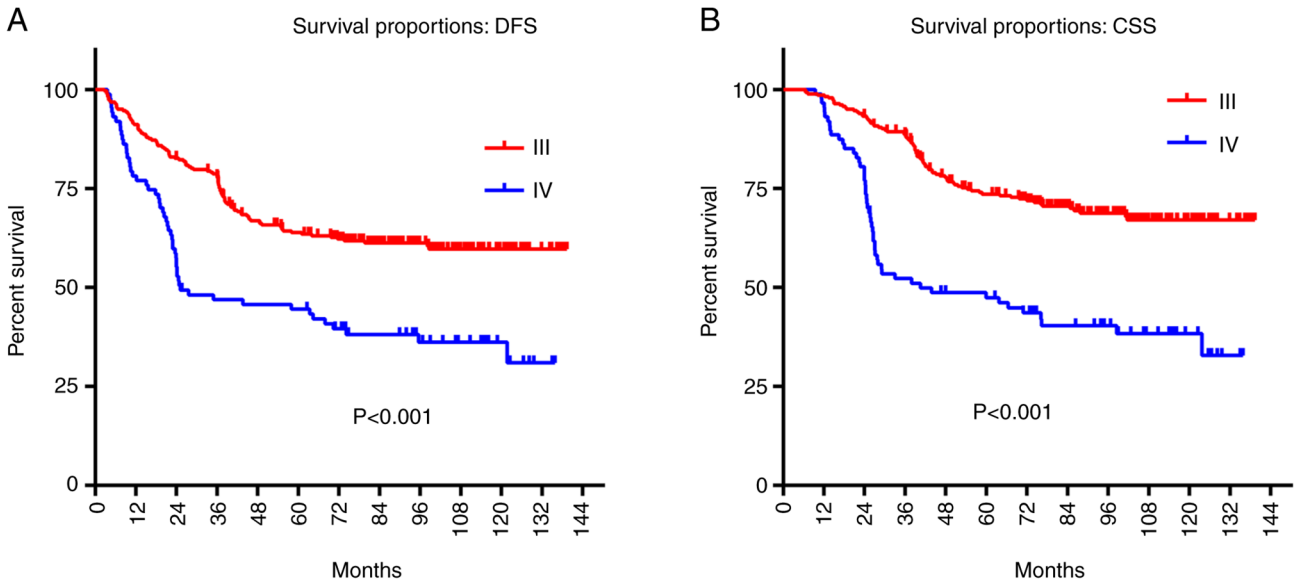

Figure 3. DFS and CSS curves stratified by cancer stage (stage II or IV). (A) DFS and (B) CSS curves stratified based on clinical stage. DFS, disease free survival; CSS, cancer-specific survival.

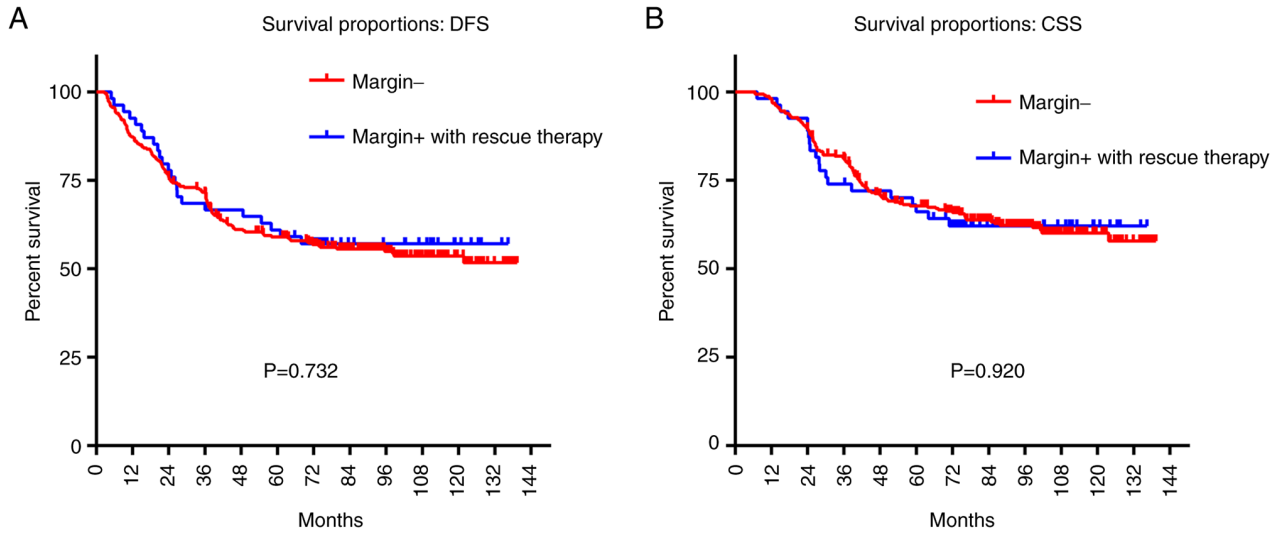

Figure 4. DFS and CSS curves stratified by margins (negative or positive surgical margins) following postoperative radiotherapy or chemoradiotherapy. (A) DFS and (B) CSS curves stratified based on margin status. DFS, disease free survival; CSS, cancer-specific survival.

respectively. In this study, the 5 -year DFS and CSS rates of patients with T3-4a N0M0 glottic LSCC stage III were better than those of stage IV patients. The prospective predictive role of radical operation was emphasized by Hinerman *et al* (25), who found a 5-year locoregional control of 56 and 89% for patients with positive and negative surgical margins, respectively. In this study, PORT or CRT was given to LSCC patients with positive margins. No significant difference was observed in the 5-year CSS and DFS rates between patients with T3-4a N0M0 glottic LSCC whose margins were negative and those whose margins were positive following rescue therapy. Hence, both PORT and CRT are useful strategies for treating patients with T3-4a glottis LSCC with positive margins.

In the present study, no significant difference was observed in the CSS and DFS rates between the T3-4a glottis LSCC patients with negative margins who underwent PORT and those who did not. These results were consistent with that described by Graboyes *et al* (3), who presented no significant difference in the CSS and OS rates of cT3N0 glottic LSCC among certain management groups (definitive RT, total laryngectomy, and total laryngectomy with adjuvant RT). Kim *et al* (6) conducted a study involving 60 T3-4 LSCC patients to assess the influence of PORT on the 5-year DFS, OS, and CSS rates. No significant difference was detected in the rates between patients who underwent primary surgery only and those who had adjuvant RT.

Although PORT is a broadly used method for treatment of patients with intermediate-advanced stage LC, delayed toxicity may later severely affect a patient's swallowing and speech function due to the regular use of RT and platinum-based chemotherapy (26) resulting in dysphagia and speech disorders. Notably, aspiration after RT for head and neck tumors is often

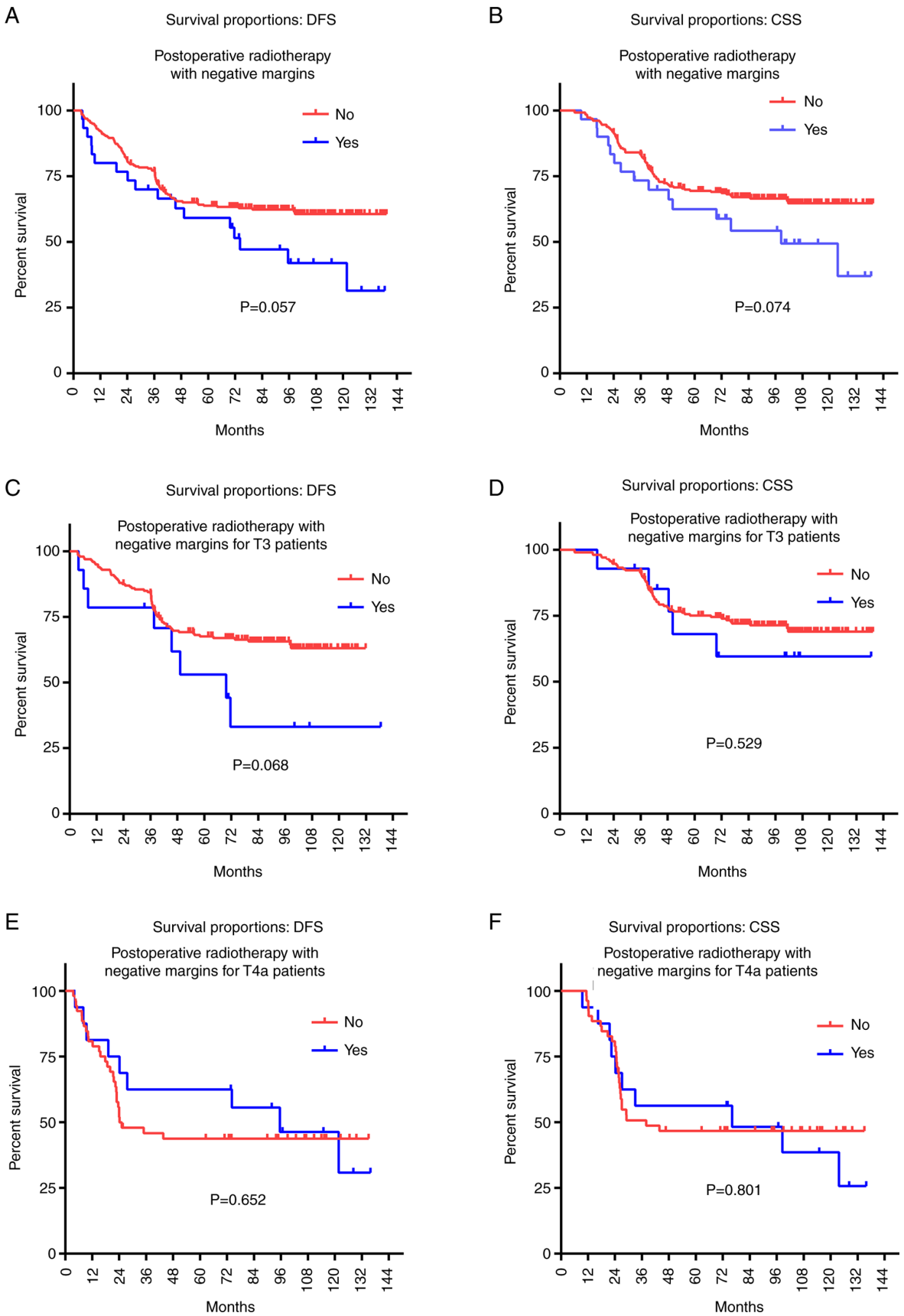

Figure 5. DFS and CSS curves of T3-4aN0M0 glottic LSCC patients stratified by administration of PORT based on margin status (negative or positive surgical margins). (A) DFS curves stratified based on administration of PORT in T3-4aN0M0 glottic LSCC patients with negative margins. (B) CSS curves stratified based on administration of PORT in T3-4aN0M0 glottic LSCC patients with negative margins. (C) DFS curves stratified based on administration of PORT in T3N0M0 glottic LSCC patients with negative margins. (D) CSS curves stratified based on administration of PORT in T3 glottic LSCC patients with negative margins. (E) DFS curves stratified based on administration of PORT in T4aN0M0 glottic LSCC patients with negative margins. (F) CSS curves stratified based on administration of PORT in T4aN0M0 glottic LSCC patients with negative margins. DFS, disease free survival; CSS, cancer-specific survival; PORT, postoperative radiotherapy.

unnoticeable because of an ineffective cough reflex in those patients, leading to death from aspiration pneumonia (27,28). A ~20% decline in the 5-year survival rates of locally advanced glottic tumor patients was detected from 1977 to 2003. There was an increase in the number of CRT procedures for all-stage glottic tumors between 2003 to 2006, which seemed to be consistent with the timing of the publication of the RTOG 91-11 and VA laryngeal studies (29,30). Nevertheless, the use of CRT for T4 cancers has been significantly reduced since 2006, possibly consistent with reports suggesting that the decrease in survival rates in laryngeal tumor patients might be driven by advanced malignancies increasingly being cured without surgery (11,31).

Researchers have questioned the role of PORT for T3 N0-1 LSCC patients cured following the operation (3,32), primarily as RT may severely influence the functional results after laryngeal operation, eventually reducing the quality of life (7).

During the present study, T3-4aN0M0 glottic patients with negative margins who did not receive PORT tended to have a better survival rate than those who received PORT. This trend was especially evident in the 10-year survival rate (DFS: 41.9 vs. 60.6%; CSS: 49.4 vs. 64.7%). Lin *et al* (33) described that 70.5% of advanced tumor patients had regular operating management, and 29.5% received concurrent chemoradiotherapy (CCRT). Nevertheless, 22.4% of the CCRT patients withdrew from the treatment due to side effects, such as xerostomia, dysphagia, neutropenic fever, percutaneous endoscopic gastrostomy tube placement, and mucositis, during the course of RT (34).

This study showed that T3-4aN0 patients did not benefit from PORT, which is consistent with previously published research and single-institution research that also reported no survival advantage for these patients. In single-institution studies (6,35,36), whether T4aN0 LSCC patients benefited from the addition of PORT has sometimes been questioned. These statistics may assist decision-making regarding whether to undergo PORT for T3-4aN0M0 glottic patients with negative margins.

In this study, most patients with negative margins did not receive RT, primarily because of the physician's experience and the patient's willingness greatly influenced the regimen during the early years of treatment for LC. For patients with T3-4aN0M0 tumors that did not penetrate the perichondrium of thyroid cartilage or cricoid cartilage, certain surgeons do not recommend PORT after radical surgery (such as total laryngectomy). In addition, a considerable number of patients refused RT because of economic concerns and/or concerns regarding the side effects. Although this is inconsistent with the latest clinical guidelines, it is closer to real-world studies, and our findings also precisely show that the RT group did exhibit survival benefits after radical surgery, which may provide some guidance for future treatments.

However, this research was limited by its retrospective nature and intrinsic biases. Because the duration of this study was relatively long and different surgeons and RT physicians may have differences in surgical methods and RT standards, the mode of postoperative adjuvant therapy was not a unified standard, although this is more in line with real-world settings. In this study, the majority of the previous patients were not evaluated for performance status; thus this data was not shown in the present study. The PRT and chemotherapeutic regimens of some patients in the dataset of this study were not homogeneous and/or incomplete, and there were also some deficiencies. Future, prospective cohort studies are required to obtain more convincing clinical data.

In conclusion, tumor classification is a prognostic factor for T3-4aN0M0 glottic LSCC patients. Partial laryngectomy is still recommended for select patients without compromising survival. PORT and CRT are valid rescue therapies for T3-4aN0M0 glottic LSCC patients with positive surgical margins. However, PORT did not increase survival in surgically managed pT3-4aN0M0 LSCC patients with negative margins, and worse outcomes were observed in the 10-year survival rate with the use of PORT.

Acknowledgements

The authors would like to thank Dr Ji Li from the Department of Radiation Oncology, Eye, Ear, Nose and Throat Hospital, Fudan University, for his work on radiation therapy in patients.

Funding

This work was sponsored by the Major Clinical Research Project of Shanghai Shen-kang Hospital Clinical Development Center (grant no. SHDC2020CR6011); the Science and Technology Innovation Project of Shanghai Shen-kang Hospital Clinical Development Center (grant no. SHDC12015114); the National Natural Science Foundation of China (grant nos. 82003178, 81772878, 30801283, and 30972691); Shanghai Sailing Program (grant no. 19YF1405900), the Shanghai Municipal Key Clinical Specialty (grant no. shslczdzk00801); the Science and Technology Committee of Shanghai (grant no. 20MC1920200); the Science and Technology Commission of Shanghai Municipality (grant no. 20Y11902200); the Shanghai Anti-Cancer Development Foundation (grant no. H6001-008); and the Training Program of the Excellent Doctors of Fudan University (grant no. QT00140).

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JZ, YH, YY, XZ, LZ, HG, CX and LT were involved in the conception and design of the study, in the analysis of the data, and in the interpretation of data. JZ, YH, CX and TL drafted the manuscript and revised it for important intellectual content. All authors have read and approved the final manuscript. CX and TL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Eye, Ear, Nose, and Throat Hospital at Fudan University (approval no. 2021039). The study was conducted in accordance with the ethical standards of the committee on human experimentation of the Eye, Ear, Nose and Throat Hospital at Fudan University and that described in the Declaration of Helsinki of 1975 as revised in 1983. All patients provided informed written consent to participate in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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