

Overall survival with and without laryngeal function preservation in 580 patients with hypopharyngeal squamous cell carcinoma

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Abstract. The aims of the present study were to review the experience of different surgical reconstruction methods for hypopharyngeal squamous cell carcinoma (HSCC) and compared the survival of patients with and without laryngeal function (LF) preservation. The clinical characteristics of 580 patients were retrospectively obtained and analyzed. Survival curves were analyzed using the Kaplan-Meier method for survival and Cox models for hazard ratios (HRs) with 95% confidence intervals (CIs). LF was preserved in 403 cases and not preserved in 177 cases. The 3- and 5-year survival rates were 70.9 and 52.7%, respectively, in the LF preservation group and 48.4 and 30.5%, respectively, in the no LF preservation group. Compared with the patients without LF preservation, patients with LF preservation had a significantly reduced risk of overall death (HR=0.63, 95% CI: 0.50-0.80). LF preservation positively affects the prognosis of patients with HSCC.

Introduction

Hypopharyngeal squamous cell carcinoma (HSCC) accounts for ~5-15% (1,2) of all head and neck cancers. This neoplasm occurs most commonly in the pyriform sinus, followed by the posterior wall of the hypopharynx; it occurs less commonly in the postcricoid region (3). Smoking cigarettes and drinking

alcohol are the main risk factors for HSCC (4). HSCC is the most aggressive head and neck cancer and has the worst prognosis (5). Treating HSCC is one of the most formidable challenges in the care of patients diagnosed with malignancies (1). Even though surgical resection, radiotherapy and neoadjuvant chemotherapy have continuously improved over the past few decades, HSCC patients remain exceedingly vulnerable to disease relapse and death (6,7), and the 5-year survival rate remains no higher than 40% (5).

Because of the close proximity of anatomical structures of HSCC tumors, reconstruction of the upper digestive tract and larynx after HSCC resection is a difficult problem. It is important to offer a safe single-stage reconstruction with low morbidity and mortality, as well as good functional rehabilitation (8). Since 1978, curative hypopharyngectomy with laryngeal function (LF) preservation and reconstruction has been used at our institution to maintain deglutition, respiration, and speech function as well as improve quality of life (QOL). In the present study, we retrospectively reviewed the oncologic and functional outcomes of 580 patients with HSCC who were treated at our institution over 15 years and compared the survival of patients with or without LF preservation.

Materials and methods

Patients and data. We retrospectively searched and reviewed the patient database of the Department of Otolaryngology, Qilu Hospital of Shandong University, Jinan, China, and identified patients with HSCC who were surgically treated from January 1996 to December 2010. A total of 580 patients with biopsy-proven squamous cell carcinoma with or without local lymph node metastases were eligible for the study. We recorded and analyzed the following data: patient and tumor characteristics, diagnosis and disease stage, excision and reconstruction methods, adjuvant treatment, swallowing outcomes, respiration, and speech function, complications, and survival. All patients signed written informed consent, and this consent procedure was approved by the Institutional Review Board (IRB) of the Ethics Boards of Qilu Hospital and the study followed the Declaration of Helsinki.

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Treatment summary. All patients were treated as follows. The preoperative workup included a barium esophagogram, endoscopic examination and biopsy, enhanced cervical computed tomography (CT) and full blood count with routine serum chemistry. Tumor staging was in accordance with the International Union against Cancer (UICC, 2002) TNM classification. None of the patients received any preoperative treatment.

Surgical procedures were performed as described previously by us (3,8-12). Briefly, the thyroid cartilage cornu superius approach was chosen for primary lesions located in the pyriform sinus. The epiglottic vallecular cervical esophageal approach was chosen when the patients had advanced pyriform sinus carcinoma. The thyroid cartilage cornu superius and hyoid bone approaches were used to resect primary lesions located in the posterior wall of the hypopharynx. The thyrohyoid membrane and pyriform sinus approaches were chosen to resect postcricoid area carcinoma. A tumor margin of ≥ 1.5 cm was considered optimal. If the esophagus was invaded, the optimal distance between the tumor and the esophageal incisal edge was >3 cm. Among the patients with LF preservation, epiglottal tissue, sternohyoid myofascial flaps, thyroid perichondrium, or platysma myocutaneous flaps were most commonly used to reconstruct the larynx. Local skin flaps, pectoralis major musculocutaneous flaps, laryngotracheal flaps, stomach or colon relocation was used to reconstruct the hypopharyngo-esophagus. All patients underwent neck dissection. If the primary carcinoma invaded the midline of the pharynx or a clear diagnosis of contralateral lymph node metastasis was confirmed by physical examination or imaging presurgically, a bilateral neck dissection was performed.

All 580 patients received adjuvant radiotherapy for 20 days to 2 months after surgery. The dosage of the postoperative radiation was 50-60 Gy in 478 cases and 75 Gy in the other 102 cases who had advanced cancer or extra-capsular invasion of lymph nodes.

Follow-up. Follow-up data were obtained by phone, letter and the outpatient clinical database. Medical record review to determine the follow-up status of all patients was performed under the direct supervision of the staff head and neck surgeon. All patients were subjected to close follow-up observation every 3 months for the first year, and every 6 months thereafter. The primary endpoint in this study was overall survival (OS), which was defined as the time from first diagnosis to death or last follow-up. The time of follow-up was completely followed up for >5 years. Participants who were alive at the end of the study period or lost to follow-up were considered censored.

Statistical analysis. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistical software was used for the analyses. The association between categorical variables was analyzed using Pearson Chi-square tests or continuous correction Chi-square tests as appropriate. OS curves were drawn using the Kaplan-Meier method, and the differences between the survival curves were examined using the log-rank test. Cox univariate and multivariate analyses were performed to explore the influences of prognostic factors on OS time. The significant variables in the univariate analyses ($P < 0.05$) were then put into the multivariate analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were measured to estimate the hazard of death

Table I. Patient clinicopathological information and demographic data (n=580).

Variables	No. (%)
Age at presentation (years)	
Median	59.0
Range	26-82
Gender	
Female	54 (9.3)
Male	526 (90.7)
Primary location	
Pyriform sinus	452 (77.9)
Posterior pharyngeal wall	97 (16.7)
Postcricoid area	31 (5.4)
T category	
T1	73 (12.6)
T2	129 (22.2)
T3	207 (35.7)
T4	171 (29.5)
Node metastasis	
N0	106 (18.3)
N1	282 (48.6)
N2	160 (27.6)
N3	32 (5.5)
M category	
M0	580 (100.0)
M1	0 (0.0)
Clinical stage	
I	32 (5.5)
II	31 (5.3)
III	236 (40.7)
IV	281 (48.5)
Histologic differentiation	
Well	114 (19.7)
Moderate	242 (41.7)
Poor	224 (38.6)
Treatment	
Surgery plus radiotherapy	580 (100.0)
Death	
Yes	393 (67.8)
No	159 (27.4)
Lost to follow-up	28 (4.8)

for the individual factors. In all analyses, a two-sided $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient clinicopathological and demographic data are shown in Table I. In summary, the study cohort mainly consisted of male patients (526, 90.7%), with a median age of 59.0 years (range, 26-82 years). All the tumors originated from the pyriform sinus (452, 77.9%), posterior pharyngeal wall (97,

Table II. Pharyngo-esophageal defect reconstruction methods in cases with and without LF preservation (n=580).

Methods	Patient no. (LF preserved)				Patient no. (LF not preserved)			
	Pyriform sinus	Posterior pharyngeal wall	Postericoid area	Total	Pyriform sinus	Posterior pharyngeal wall	Postericoid area	Total
Direct suture	234	23	5	262	51	-	-	51
PMMF	65	12	-	77	11	-	-	11
Split graft	-	4	-	4	-	-	-	-
PMMF + split graft	-	7	-	7	-	-	-	-
Laryngotracheal flap	-	-	-	-	30	18	14	62
PMMF + laryngotracheal flap	-	-	-	-	7	5	-	12
Stomach pulling-up	17	-	-	17	19	11	7	37
Colon interposition	22	9	5	36	-	4	-	4

PMMF, pectoralis major musculocutaneous flap; LF, laryngeal function.

Table III. Clinical characteristics of the patients with and without LF preservation (n=580).

Characteristics	Total	Patients (LF preserved) n (%)	Patients (LF not preserved) n (%)	P-value
T category				
T1-T2	202	187 (92.6)	15 (7.4)	<0.001 ^a
T3-T4	378	216 (57.1)	162 (42.9)	
Node metastasis				
N0-N1	388	280 (72.2)	108 (27.8)	0.046 ^a
N2-N3	192	123 (64.1)	69 (35.9)	
Clinical stage				
I-II	63	59 (93.7)	4 (6.3)	<0.001 ^a
III-IV	517	344 (66.5)	173 (33.5)	
Primary location				
Pyriform sinus	452	338 (74.8)	114 (25.2)	<0.001 ^a
Posterior pharyngeal wall	97	55 (56.7)	42 (43.3)	
Postericoid area	31	10 (32.3)	21 (67.7)	

^aP<0.05.

16.7%), and postericoid area (31, 5.4%) and most patients had advanced T-stage disease (T3-T4, 65.2%), lymph node metastasis (81.7%), and advanced clinical stage disease (stage III and IV, 89.2%). There were no cases of distant metastasis. Pathological studies confirmed that 114 cases (19.7%) were well differentiated, 242 cases (41.7%) were moderately differentiated and 224 cases (38.6%) were poorly differentiated.

LF was preserved in 403 cases and not preserved in 177 cases. All the patients underwent modified neck dissection, including both unilateral (412 patients) and bilateral (168 patients) dissections. As shown in Table II, pharyngo-esophageal defect reconstruction methods in cases with LF preserved were as follows: direct suture in 262 patients, pectoralis major musculocutaneous flap in 77, split graft in 4, pectoralis major musculocutaneous flap combined with the split graft in 7, stomach pulling-up in 17, and colon interposition in 36 patients.

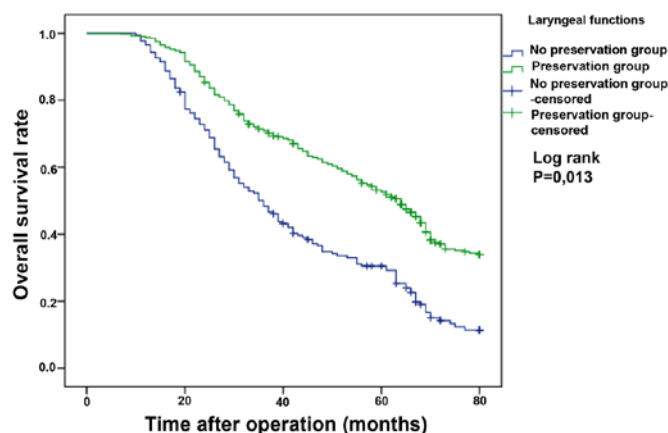


Figure 1. Kaplan-Meier curves for survival of the patients with and without LF preservation.

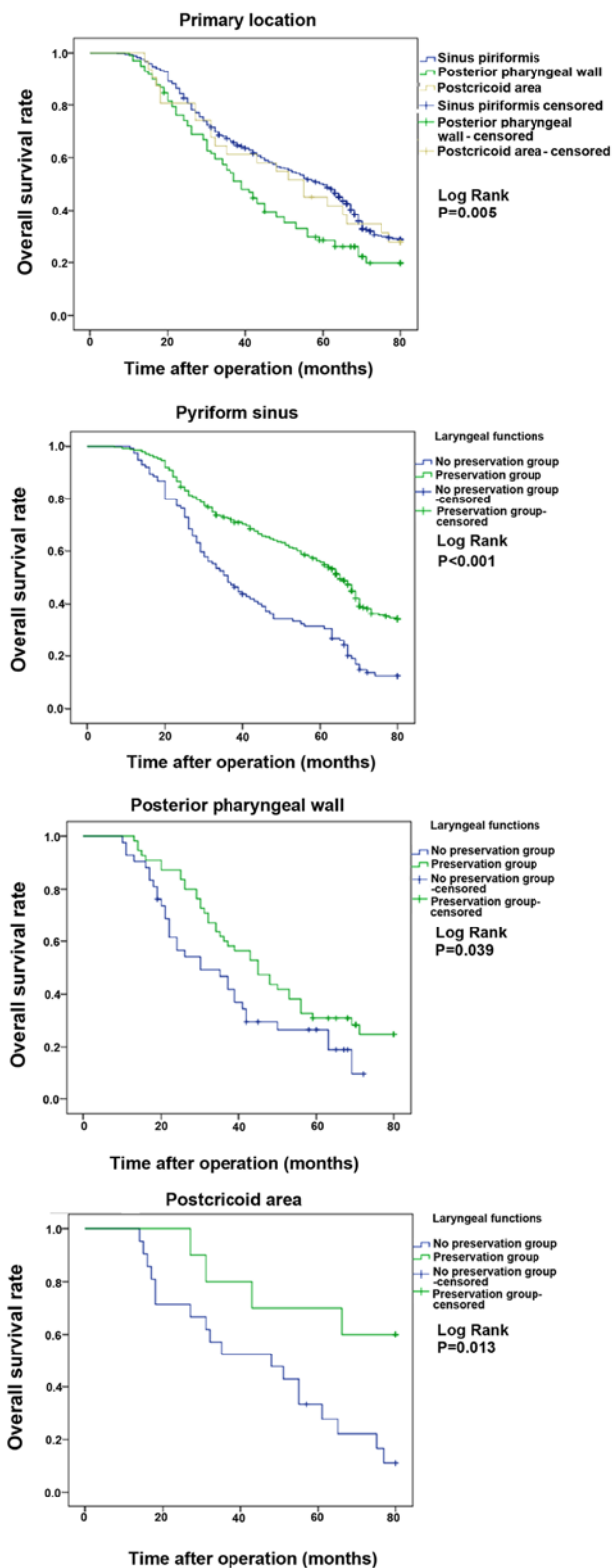


Figure 2. Kaplan-Meier curves for survival according to primary location.

In cases without LF preservation the methods included: direct suture in 51 patients, pectoralis major musculocutaneous flap in 11, laryngotracheal flap in 62, laryngotracheal flap combined with pectoralis major musculocutaneous flap in 12, stomach reposition in 37 and colon interposition in 4 patients. Among the 403 cases with LF preservation, 122 cases did not need laryngeal reconstruction since the laryngeal integrity was

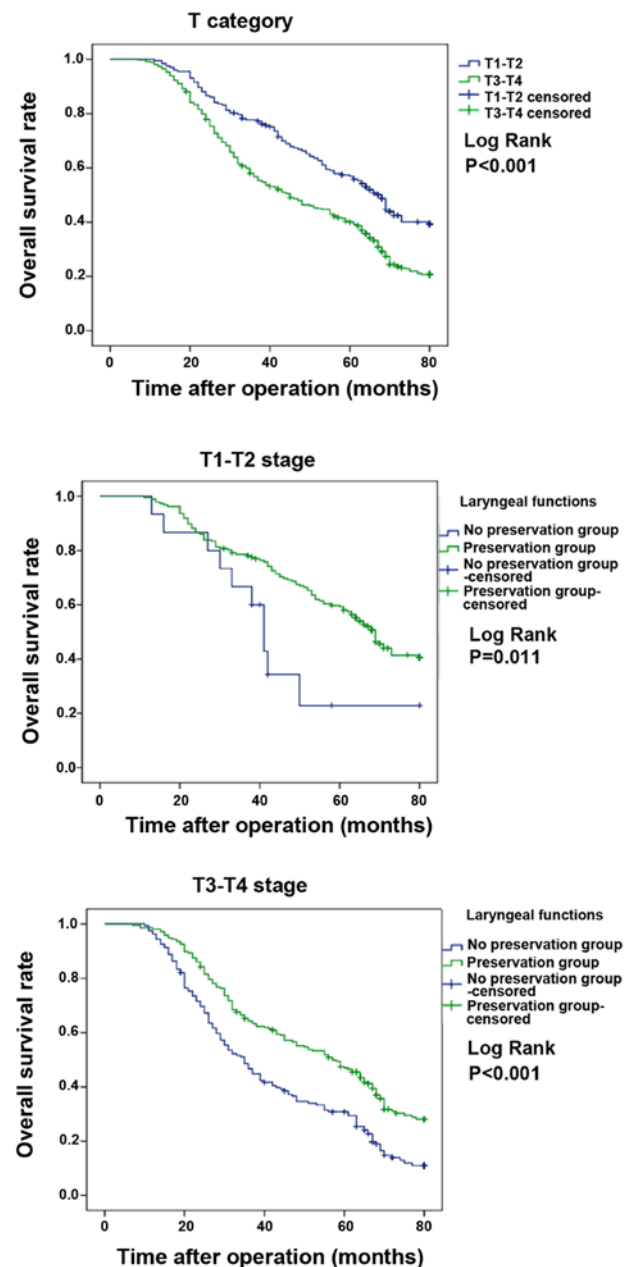


Figure 3. Kaplan-Meier curves for survival according to T category.

maintained; the other 281 cases were reconstructed using the epiglottis (170 cases), sternohyoid myofascial flap (48 cases), thyroid perichondrium (42 cases), or platysma myocutaneous flap (21 cases). Laryngeal functions (voice, respiration and deglutition) were completely restored in 286 (71.0%) patients and partially restored (voice and deglutition) in 117 (29.0%) patients.

There were significant statistical differences between the LF preservation group and the group without LF preservation in regards to T stage ($P<0.001$), N stage ($P=0.046$), clinical stage ($P<0.001$) and tumor site ($P<0.001$) (Table III). The overall 3- and 5-year OS rates were 64.0 and 45.9%, respectively. The 3- and 5-year OS rates in the LF preservation group were 70.9 and 52.7%, respectively, while in the group without LF preservation, the 3- and 5-year OS rates were 48.4 and 30.5%, respectively (Fig. 1). OS rates according to tumor site (Fig. 2), T stage (Fig. 3), lymph node metastasis (Fig. 4) and clinical

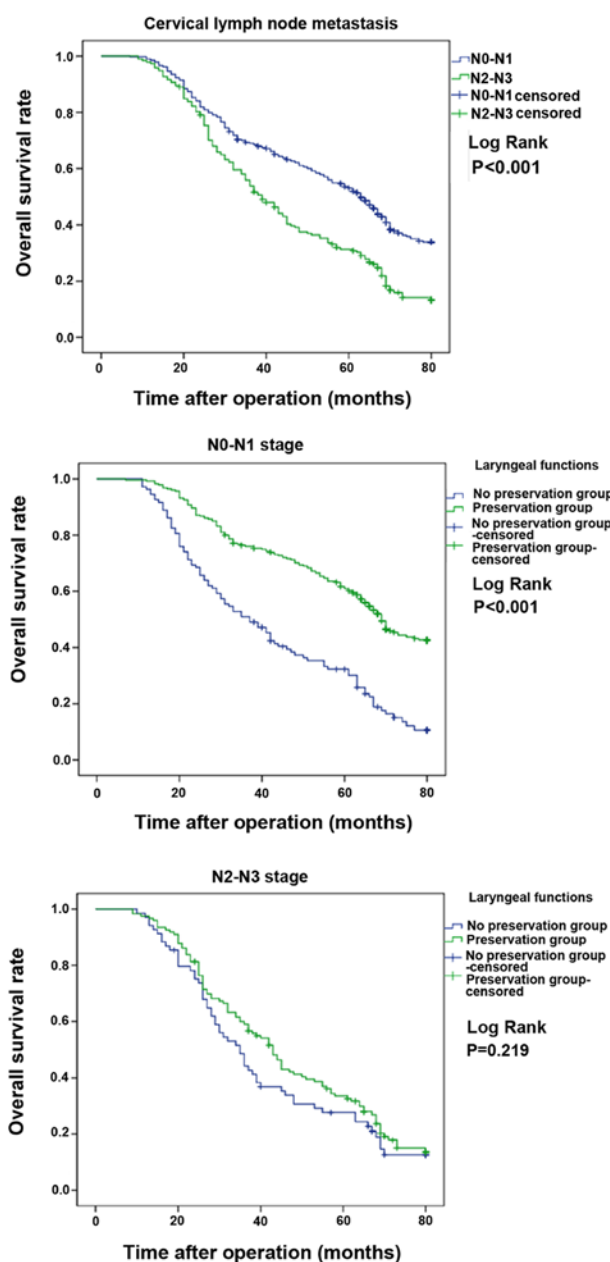


Figure 4. Kaplan-Meier curves for survival according to cervical lymph node metastasis.

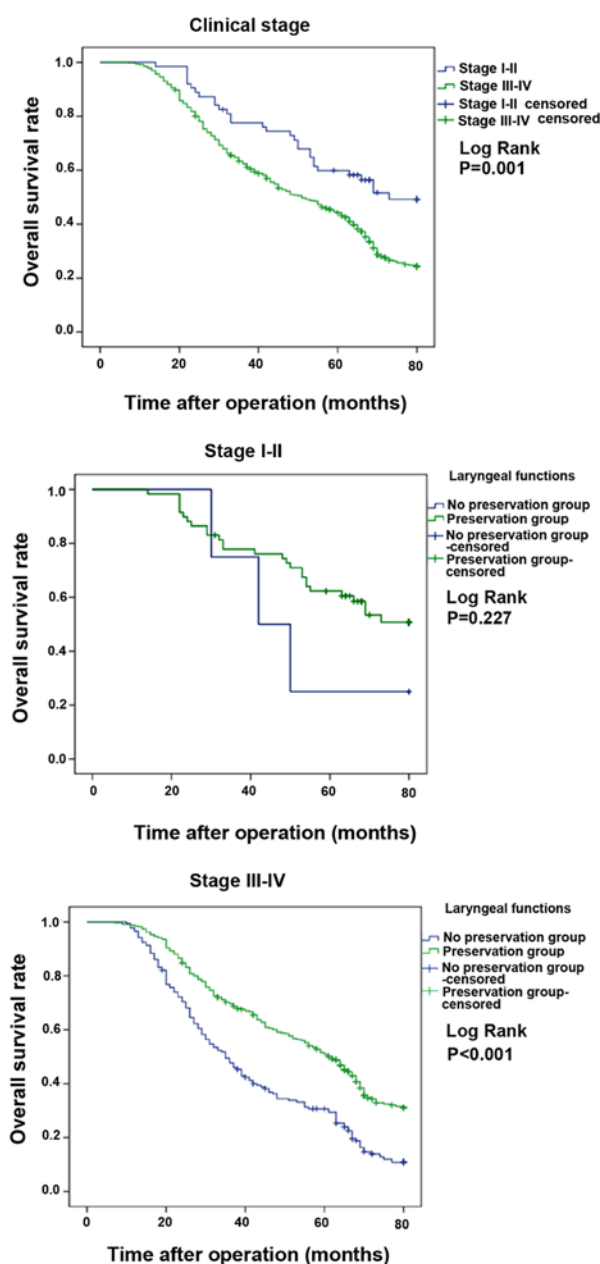


Figure 5. Kaplan-Meier curves for survival according to clinical stage.

stage (Fig. 5) among patients with and without LF preservation are shown in Table IV.

Multivariable Cox proportional hazards regression analysis was performed to evaluate the association between LF preservation and overall risk of death in the patients with HSCC. The adjusted confounders were T stage, N stage, clinical stage, differentiation and treatment. As shown in Table V, compared with the patients without LF preservation, patients with LF preservation had a significantly reduced risk of overall death (HR=0.633, 95% CI: 0.503-0.797).

Discussion

In the present study, we found that patients with LF preservation had significantly higher OS rates than did patients without LF preservation, and LF preservation significantly reduced

the risk of overall death. The 3- and 5-year OS rates were 70.9 and 52.7%, respectively, in the LF preservation group and 48.4 and 30.5%, respectively, in the group without LF preservation. Although LF preservation is often performed in cases of relatively less advanced tumors, however, as the Cox multivariate analysis confirmed, LF preservation itself can improve survival. This may be due to the relatively high QOF after surgery.

LFs (voice, respiration and deglutition) were completely restored in 286 (71.0%) patients and partially restored (voice and deglutition) in 117 (29.0%) patients with LF preservation. The success of organ preservation relies not only on favorable survival and preservation rates but also on adequate function of the remaining organ. Before the decision to attempt LF preservation is made, X-ray barium meal examination, enhanced cervical CT and laryngoscopy are used to determine

Table IV. Overall survival rates according to tumor site, T stage, lymph node metastasis, and clinical stage among the patients with and without LF preservation (n=580).

Variables	3-year survival rate (%)			5-year survival rate (%)		
	LF preserved	LF not preserved	Total	LF preserved	LF not preserved	Total
Primary location						
Pyriform sinus	72.4	48.2	66.3	55.8	31.7	49.7
Posterior pharyngeal wall	60.0	46.7	54.3	30.9	26.5	28.5
Postcricoid area	80.0	52.4	61.3	70.0	33.3	45.2
T category						
T1-T2	78.6	66.7	77.7	59.2	22.9	56.9
T3-T4	64.2	46.6	56.7	47.0	30.8	40.0
Node metastasis						
N0-N1	76.0	50.9	69.0	61.0	32.3	53.0
N2-N3	59.1	44.2	53.8	33.5	27.6	31.4
Clinical stage						
I-II	77.9	75.0	77.7	62.3	25.0	59.9
III-IV	69.7	47.7	62.4	51.0	30.7	44.2

Table V. Results of the univariate and multivariate Cox regression analyses in 580 patients with and without LF preservation.

Parameters	Comparison	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR ^a	95% CI	P-value
Age (years)	<60 vs. ≥60	1.12	0.92-1.37	0.249			
Gender	Male vs. female	1.37	0.99-1.89	0.056			
T stage	T1-T2 vs. T3-T4	1.71	1.37-2.13	<0.001 ^b	1.32	1.03-1.67	0.026 ^b
Node metastasis	N0-N1 vs. N2-N3	1.90	1.55-2.33	<0.001 ^b	1.62	1.31-2.00	<0.001 ^b
Differentiation	Poor vs. well and moderate	1.20	1.05-1.37	0.007 ^b	1.15	1.00-1.32	0.047 ^b
Clinical stage	I-II vs. III-IV	1.89	1.30-2.75	0.001 ^b	1.23	0.81-1.87	0.331
Treatment	LF not preserved vs. LF preserved	0.49	0.40-0.61	<0.001 ^b	0.63	0.50-0.80	<0.001 ^b

^aHR (hazard ratio), adjusted by age, gender, staging, treatment and primary location. ^bP<0.05. CI, confidence interval.

the optimal range of surgery. The complete resection of the tumor and the preservation of a maximum amount of laryngeal tissue are the key factors considered when we consider the feasibility of LF preservation. We think that patients with at least one movable arytenoid cartilage and a normal contralateral pyriform sinus can undergo LF preservation. However, during surgery, tumors should be fully exposed to the naked eye, and it is unwise to reduce the scope of surgery for the protection of LF. In addition, respiratory function tests and cardiologic examination are also important. For elderly or weak patients and those with poor cardiopulmonary function, LF preservation is unsuitable, even if there is enough remnant laryngeal tissue. Four patients in the present study, although with clinical stage I-II disease, were unable to undergo LF preservation owing to their poor cardiopulmonary function.

The main purpose of reconstruction of LF is to prevent aspiration after surgery. In our previous study, we reported several LF reconstruction methods in detail (3): i) if the

epiglottis was resected completely, the tongue flap covered the laryngeal inlet and the pyriform sinus was capacious to help the food pass the laryngeal inlet as quickly as possible to avoid aspiration; ii) if the majority of the supraglottic tissues on the same side as the tumor were resected, the epiglottis was pulled downward or rotated outwards in order to suture it with the surgical margin of subglottic tissues and to re-shape the lateral wall of the residual larynx; iii) if the edge of the epiglottis was involved by tumor, the remnant epiglottis was pulled downward to reconstruct the lateral wall of the laryngeal vestibule and to cover the laryngeal inlet effectively; iv) because LF preservation in the postcricoid area is troublesome, if the bilateral arytenoid cartilage is movable and the interarytenoid notch is not infiltrated, the carcinoma can be resected completely without total laryngectomy and v) the sternohyoid myofascial flap, thyroid perichondrium, or platysma myocutaneous flap could be inverted into the laryngeal cavity to repair the defects of the larynx.

The most important aspect of pharyngo-esophageal defect reconstruction is to create/maintain a spacious cavity in the hypopharynx so that food can pass more quickly and smoothly and aspiration will be less likely. It is important to deal appropriately with the laryngeal inlet rather than to rebuild the affected ipsilateral part of the pyriform sinus. For early stage tumors, the remnant mucosa can be sutured directly to close the hypopharyngeal cavity. However, for advanced-stage tumors, if the excised tissue exceeds the ipsilateral area in the pyriform sinus and extends to the posterior wall of the hypopharynx, postcricoid area, or cervical esophagus, reconstruction of the hypopharynx should involve use of a local skin flap, pectoralis major musculocutaneous flap, or stomach reposition or colon interposition with vessel pedicles. In cases with removal of one side of the lateral wall of the cervical esophagus and tumor involvement limited to within 3 cm below the inlet of the esophagus, a pectoralis major musculocutaneous flap is still suitable to repair the defect. However, the anastomotic orifice should be formed obliquely to prevent anastomosis from stenosis (13). If the cervical esophagus is involved more than 3 cm below the inlet of the esophagus, the use of a pectoralis major musculocutaneous flap is difficult because the esophageal incisal margin is below the superior aperture of the thorax. In that case, stomach repositioning or colon tissue interposition with vessel pedicles is more appropriate in our experience (12). For elderly or weak patients and those with poor cardiopulmonary function, LF preservation is unsuitable. Thus, in those cases, the hypopharynx can be reconstructed using a laryngotracheal flap.

Pharyngocutaneous fistulas were observed in 34 patients in our study. After postoperative nutrition and wound dressing were improved, 26 patients healed spontaneously within 4 weeks; 4 patients healed by two-stage suture, and 4 patients underwent reconstruction with a pectoralis major musculocutaneous flap. Pharyngocutaneous fistula is the most common complication occurring after head and neck surgery. It may lead to high surgical morbidity and mortality rates, prolonged hospital stays, high hospital costs, and increased emotional distress. It may also prevent or delay the onset of radiation therapy and patient rehabilitation. In our experience, the occurrence of pharyngocutaneous fistula can be prevented by: i) using negative pressure drainage; ii) ensuring that the remnant mucosa is fixed to the submucosal tissue and/or posterior part of the ipsilateral thyroid cartilage, which can prevent suture dehiscence and iii) reducing the tissue defect lateral to the anastomotic orifice by using a thyroid gland, uni-pedicated sternohyoid myofascial, or uni-pedicated sternocleidomastoid myofascial flap.

In conclusion, we retrospectively reviewed a series of 580 HSCC patients who were treated with surgery followed by radiotherapy at our institution. Although most patients presented with advanced clinical stage disease, the majority of the patients could be surgically treated with LF preservation. LF preservation may affect prognosis and QOL: patients with LF preservation had significantly better survival and QOL than those without LF preservation. Although there is disagreement about which multidisciplinary plan [radiotherapy followed by surgery, surgery followed by radiotherapy, induction chemotherapy followed by radiotherapy, or concurrent chemotherapy and radiotherapy (14,15)] is best for HSCC patients, we recommend the comprehensive use of surgery and radiotherapy.

However, further investigations that take into account early diagnosis and novel effective therapies are still needed.

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