

# Therapeutic effect on pyriform sinus carcinoma resection via paraglottic space approach: Results of a single-centre study of 93 patients

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## Abstract

**Objective** To analyse the surgical indications, surgical efficacy and key influencing factors of prognosis of using a novel surgical approach for pyriform sinus carcinoma resection utilising the paraglottic space. **Methods** From 2014 to 2017, 93 patients with squamous cell carcinoma originating in the pyriform sinus were resected through the paraglottic space approach. The postoperative laryngeal function preservation, complications, survival rate and prognostic factors were analysed. **Results** The 2, 3 and 5 year overall survival rates of the patients were 77.2%, 61.6% and 47.4%, respectively. The univariate analysis of survival rate showed that primary tumour T stage and N stage had a statistically significant effect on the survival rate of patients ( $P=0.047$  and  $P<0.001$ , respectively). Multivariate analysis with the Cox regression model revealed that N stage is an independent risk factor for postoperative survival ( $P=0.042$ ). The preservation rate of laryngeal function was 65.6% (61/93). Pharyngeal fistula incidence was 4.3% (4/93). Systemic distant metastasis and second primary cancer were found to be the main causes of death. **Conclusions** As a novel surgical approach for the resection of pyriform sinus carcinoma, the paraglottic space approach can better expose the tumour, effectively improve the retention rate of laryngeal function, reduce the incidence of pharyngeal fistula and result in the better recovery of postoperative swallowing function with satisfactory long-term survival. This surgical approach can be applied in patients with lesions that do not involve the paraglottic space. N stage is an independent risk factor for postoperative survival. **Key Points:** In this study, we present a novel surgical approach for hypopharyngeal carcinoma resection utilizing the paraglottic space. The paraglottic space is a natural anatomical space. If the thyroid cartilage plate is cut obliquely and pulled posterolaterally, the paraglottic space can be easily exposed. The paraglottic space approach can help expose neoplasms under direct vision and save mucosa during surgery while sufficiently preserving laryngeal function. In our study, application of the paraglottic approach significantly reduced one of the serious postoperative complications, pharyngocutaneous fistula. This approach can be proposed as a promising candidate for resection of early T stages of hypopharyngeal carcinoma.

## Introduction

Hypopharyngeal cancer is a highly malignant tumour of the head and neck that accounts for approximately 3%–5% of all head and neck malignancies [1]. The pyriform sinus is the most frequently affected site and represents 70% of hypopharyngeal carcinoma [2]. Given the close location of the pyriform sinus to the larynx, pyriform sinus cancer easily invades the larynx, resulting in the destruction of laryngeal structure and function. Considering that accurate tumour resection is needed to achieve local control and improve survival rate, how to preserve laryngeal function as much as possible to improve the quality of life of patients after surgery is a difficult problem. Previously, we explored and summarised a new surgical approach, namely, the paraglottic space approach, through clinical practice to remove pyriform sinus carcinoma. This approach achieved good results in clinical practice. In this paper, we retrospectively analysed the clinical data of patients admitted to our department from 2014 to 2017 who underwent pyriform sinus carcinoma resection

via the paraglottic space approach. The purpose of this study was to summarise and explore the surgical indications, therapeutic effects, surgical advantages and influencing factors of this approach for pyriform sinus carcinoma resection.

### Materials and methods

The clinical data of 93 patients who underwent primary pyriform sinus carcinoma resection via the paraglottic space approach, from January 2014 to January 2017 were retrospectively analysed. All patients were operated for the first time without preoperative chemoradiotherapy and underwent electronic laryngoscopy, narrow band imaging, electronic gastroscopy and cervicothoracic enhanced CT before surgery. Patients with distant metastasis or second primary cancer and general anaesthesia contraindications were excluded from this study. The age of the patients ranged from 41 years to 87 years. Amongst the 93 patients, 91 were males and 2 were females with an average age of  $58.8 \pm 9.51$  years. The general clinical data and tumour characteristics of all patients (in accordance with the American Joint Committee on Cancer 2017 8th edition TNM staging of hypopharyngeal carcinoma) are summarised in Tables 1–2. The STROBE standard reporting guidelines for cohort studies were followed.

Table 1. T N Stage

	N0	N1	N2	N3	
T1	5	2	0	0	7
T2	10	6	8	1	25
T3	7	9	25	2	43
T4	2	4	12	0	18
	24	21	45	3	

Table 2. Population and Cancer Data

Data	n (%)	X <sup>2</sup>	P
Gender		1.545	0.214
Male	91		
Female	2		
Age(y)		1.111	0.292
≥60	50		?
<60	43		
Cigarette smoking		0.233	0.629
Ever	82		
Never	11		
Alcohol drinking		1.304	0.253
> 50 g/d	84		
< 50 g/d	9		
Tumour differentiation degree		3.909	0.142
Well	9		
Moderately	29		
Poorly	55		
Initial location of cancer in the pyriform sinus		2.612	0.271
Medial wall	56		
Lateral wall	18		
lateral and medial walls	19		
laryngeal function preservation	61	1.661	0.197
AJCC stage		7.017	0.071
I	5		

II	10
III	24
IV	54

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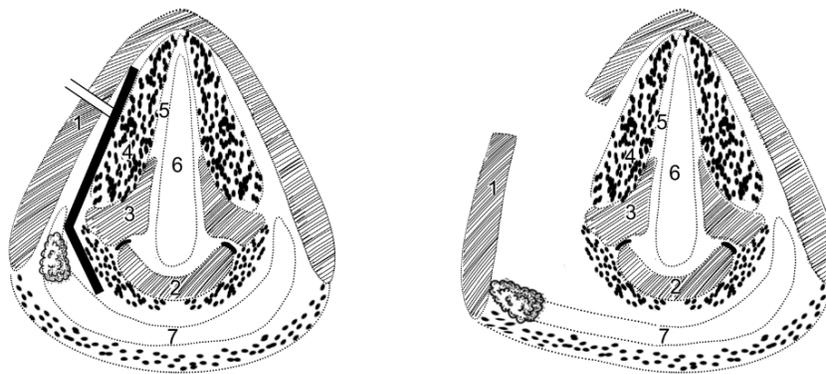
## Description of the surgical procedure

The neck dissection method was selected in accordance with the preoperative examination, primary tumour extent and regional lymph node metastasis. Patients with N0–N1 underwent ipsilateral II–IV selective neck dissection, patients with N2 underwent ipsilateral II–V neck dissection, and patients with N3 underwent ipsilateral I–V + contralateral II–IV neck dissections. If the tumour crosses the midline, bilateral neck dissection is performed; level VI and retropharyngeal lymph node dissections were performed for patients with T3–T4 and N2b or above.

### 1. Tumour resection method

After the neck lymph node dissection was completed, the free cervical sheath was pulled outward, the ipsilateral thyroid lobe was separated, and the ipsilateral great horn of the hyoid bone was removed. The inferior constrictor of the pharynx was cut off on the surface of the thyroid cartilage plate, and the thyroid cartilage plate was obliquely incised so that the thyroid cartilage plate was divided into two parts: anterior 2/3 and posterior 1/3. The piriform sinus was gradually separated from the larynx by pulling the posterior part of the thyroid cartilage plate outward and removing the connective tissue along the lateral surface of the thyroarytenoid muscle, and the paraglottic space was easily exposed (Fig. 1).

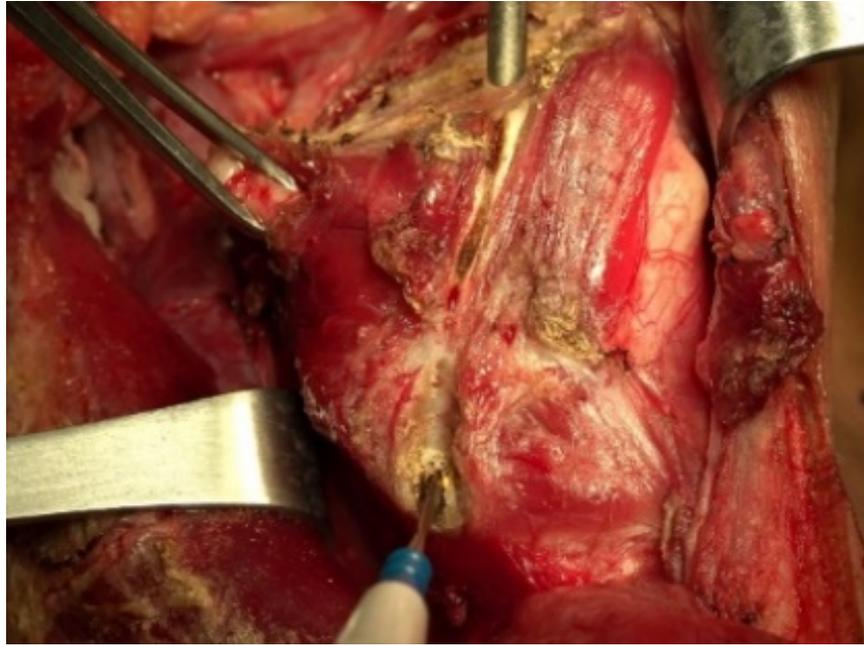
For the carcinoma of the lateral wall of the piriform sinus, the thyroid cartilage plate was pulled outward, and the ipsilateral piriform sinus can be separated from the larynx through the paraglottic space approach. The tumour was fully exposed and resected under direct vision, and all the cutting edges were sent for frozen pathology until the negative margin was obtained. For the carcinoma of the medial wall of the piriform sinus, the lateral surface of the thyroarytenoid muscle was fully skeletonised until the arytenoid cartilage appeared. Firstly, the resection of the deep margin of the tumour was completed. Subsequently, the tumour was removed under direct vision by entering the pharyngeal cavity naturally through the free edge of the aryepiglottic fold or through the posterior incision of the thyroid cartilage plate into the pharyngeal cavity (critical surgical steps were shown in Fig. 2, (Such as Video1)). If the paraglottic space was involved during the operation, partial laryngectomy or total laryngectomy was performed selectively.



**Figure1 schematic diagram of paraglottic space approach**

Horizontal section of larynx at the level of the glotti

1=thyroid cartilage,2=cricoid cartilage,3=arytenoid cartilage,  
4=thyroarytenoid muscle,5=vocal cord, 6= airway lumen,7=lumen of the hypopharynx  
black solid line=paraglottic space, double slash=Incision of thyroid cartilage



**Figure2** Pictures of surgical procedures

**A** Exposure of lateral edge of thyroid cartilage plate.**B** After the moderate outwards traction and lysis of the surrounding tissue, the paraglottic space was exposed. **C** Enter the pharyngeal cavity from the paraglottic space and remove the tumour under direct vision. **D** Remove the tumour along the safe boundary of the tumour. **E** the mucosa of the posterior wall of the hypopharynx is sutured up and down to widen the pharyngeal cavity.**F** Suture the pharyngeal mucosa and close the pharyngeal cavity

## 2. Repair

For stage T1 and T2 lesions, the pharyngeal cavity can mostly be closed with local mucosal pulling sutures after tumour resection. For stage T3 and T4 lesions, such as the tumour of the lateral wall of the piriform sinus invading the posterior wall of the hypopharynx or the tumour invading the entrance of the oesophagus, the defect of the lateral wall of the pharynx is so large that it is difficult to pull and suture directly after tumour resection. The most common method we use to repair the pharyngeal cavity is pedicled pectoralis major myocutaneous flap (Such as Video2). In addition, after the pharyngeal cavity was closed, the ipsilateral uninvolved thyroid lobe was lifted and fixed on the lateral side of the pharyngeal suture to strengthen the pharyngeal wall and reduce the incidence of pharyngeal fistula.

## 3. Postoperative adjuvant chemoradiotherapy

Postoperative radiotherapy alone was performed in 70 cases, whereas postoperative concurrent chemoradiotherapy was performed in 18 cases. The target areas of radiotherapy included the primary focus and the cervical lymphatic drainage area. All patients were treated with intensity-modulated radiotherapy (IMRT). The dose of radiotherapy was 50–66 Gy/25–33 f, 1.8–2.0 Gy/f, 5 f/W. The concurrent chemotherapy regimen was combined chemotherapy based on cisplatin.

## Follow-up and statistical analysis

The survival stage and prognosis of all patients were followed up by means of telephone return visits, outpatient reexaminations, and other methods. Follow-up period was once every 3 months in the first and second years and once every 6 months in the third to fifth years. The re-examination included physical examination, laryngoscopy and imaging examination (cervicothoracic enhanced CT). Patients with clinically suspected tumour recurrence were examined by PET–CT. Survival rate was analysed via Kaplan–Meier analysis. The difference between groups was tested through log-rank method, and independent prognostic factors were analysed by Cox regression model in multivariate survival analysis. The statistical software SPSS 25 was used to analyse the data.  $P < 0.05$  was considered statistically significant.

## Results

### Postoperative data of patients

All patients were followed up for 5 years. Six patients were lost by the end of follow-up. Survival analysis was performed in accordance with the final follow-up time. The follow-up time was 6–82 months, and the median follow-up time was 50 months. The patients who lost follow-up participated in the survival analysis as censored data, and the survival time was calculated according to the last follow-up time before the loss of follow-up. The postoperative pathology of all patients was squamous cell carcinoma. The metastasis rate of lateral cervical lymph nodes was 74.2% (69/93). Seventy patients underwent level VI lymph node dissection and retropharyngeal lymph node dissection. The positive rates of region VI lymph nodes and retropharyngeal lymph nodes were 12.9% (9/70) and 15.7% (11/70), respectively.

A total of 78 patients in this group had their larynges preserved. 11 patients underwent tongue root flap repair, 20 patients underwent pectoralis major myocutaneous flap repair, and 5 patients underwent subchin flap repair. Other patients performed local mucosal flap repair of pharyngeal defects.

Pathological examination revealed that 81 patients (87%) had negative tumor margins without lesions. Twelve cases had positive or poorly defined margins microscopically, and in these cases, the margins of the frozen sections were expanded until the margins were negative.

By postoperational laryngeal function evaluation methods such as subjective sensation, voice quality, electronic laryngeal endoscopy, and X-ray barium meal examination, 65.6% (61/93) cases showed complete recovery of laryngeal functions (speech, respiration, and deglutition). shown in Table 3.

Tracheal cannula removal time. Amongst the 78 patients with laryngeal preservation, 63 patients were extubated after radiotherapy. Unfortunately, 2 patients underwent tracheotomy and intubation again with laryngeal edema.

During the perioperative period, four cases had internal pharyngeal fistula, two cases experienced subcutaneous effusion, and one case experienced bleeding at the tracheotomy, all of which were cured by dressing change and pressure bandaging. One case of pulmonary infection improved after switching to sensitive antibiotics. No death occurred during the perioperative period.

T grade	The preservation of laryngeal functions in different T stage	The preservation of laryngeal functions in different T grade
T1-T2		Laryngeal preservation Yes (78 cases)
T3		32
T4		37
Total		9
		78

### Survival and prognostic factor analyses

The Kaplan–Meier survival curve method provided a 2-year survival rate of 77.2%, a 3-year survival rate of 61.6% and a 5-year survival rate of 47.4%. Univariate analysis was carried out in accordance with the

general data, tumour characteristics and TNM stage of the patients. The results of log-rank test showed that sex, age, history of smoking and alcohol, degree of tumour differentiation, primary site, clinical stage and preservation of laryngeal function were all  $P > 0.05$ , which indicates no statistical significance (Table 2). However, significant differences in survival were found between stages T1–T2 and T3–T4 ( $\chi^2 = 3.959$ ,  $P = 0.047$ ) and amongst N0–N3 ( $\chi^2 = 17.767$ ,  $P < 0.001$ ; Fig.3). The Cox regression analysis of tumour differentiation based on primary site, clinical stage, T and N stages and preservation of laryngeal function revealed that N stage is an independent risk factor of pyriform sinus carcinoma resected via the paraglottic space approach ( $P = 0.042$ , Fig.3).

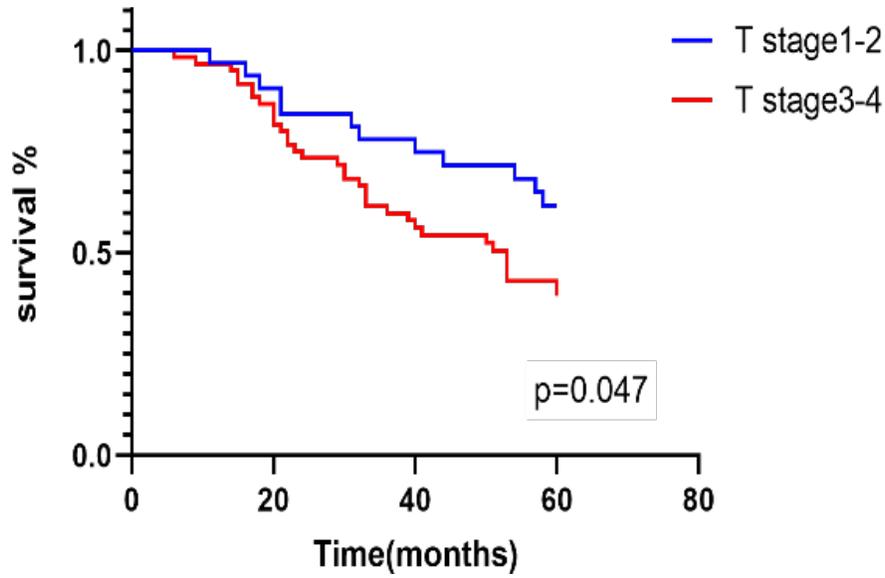


Figure3 Kaplan-Meier survival curves for different T-stages and N-stages

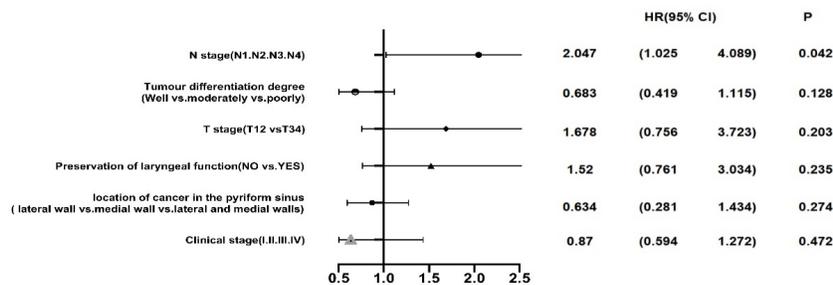


Figure3 Multivariate regression analysis of factors influencing overall survival.

### Cause of death

Fifty-one patients died as of the last follow-up date. The main causes of death included systemic distant metastasis (18 cases, 35.3%), including lung metastasis (9 cases), liver metastasis (5 cases), bone metastasis (3 cases) and brain metastasis (1 case); second primary cancer (11 cases, 21.6%), including middle and lower oesophageal cancers (7 cases), central lung cancer (3 cases) and gastric cancer (1 case) and nontumour causes of death (9 cases, 17.6%), including respiratory failure (3 cases) and cardiogenic death (2 cases),

severe pneumonia (1 case), asphyxia caused by sputum thrombus (1 case) and unknown causes (2 cases). Local metastases of cervical lymph nodes were found in 7 cases (13.7%). Local tumour recurrence was found in 6 cases (11.8%).

## Discussion

The paraglottic space is a potential space containing adipose tissue and blood vessels, bordered laterally immediately adjacent to the thyroid cartilage, medially adjacent to the thyroarytenoid muscle and bordered dorsally to the piriformis sinus [3]. The paraglottic space can be easily exposed if the thyroid cartilage plate is cut obliquely during the operation and the posterior part of the thyroid cartilage plate is pulled outward (such as the description of the previous surgical method). The advantages of the paraglottic space approach are as follows. The paraglottic space is a natural anatomical space, and the tissue is easily separated through the paraglottic space approach with less intraoperative blood loss and a clear surgical field. The hypopharynx is easier to separate from the larynx and the highly wrinkled pharyngeal cavity is easily planarised to fully expose the tumour and removing the tumour in a 3D way under the full dissociation of the mucous membrane through the paraglottic space approach. The tumour is not squeezed in the process of surgical resection, which is in line with the principle of tumour resection. The surgical field of view via the paraglottic space approach is well exposed. Combined with the preoperative narrow band imaging examination, the tumour can be accurately removed under direct vision, and the normal hypopharyngeal mucosa can be preserved as much as possible, which is conducive to pharyngeal cavity reconstruction and function preservation.

How to improve the retention rate of laryngeal function without affecting the survival rate of patients has become the focus of clinical attention. Relevant scholars also confirmed the feasibility of laryngeal function-preserving surgery for pyriform sinus carcinoma and provided a pathological basis [4-6]. The National Comprehensive Cancer Network guidelines point out that surgery is feasible for patients with T1+N positive and T2-3Nx hypopharyngeal cancer to preserve the laryngeal structure, and partial laryngectomy (open or laser) combined with postoperative radiotherapy can be considered. These patients are expected to preserve laryngeal function. Although a part of pyriform fossa carcinoma belongs to T4, only the posterior edge of the thyroid cartilage, a small part of the cricoid cartilage, or the entrance of the cervical esophagus are involved. After tumor resection, most of the larynx can be preserved, the pectoralis major myocutaneous flap can be used to reconstruct the pharyngeal cavity, and the preservation of laryngeal function can be realised.

The paraglottic space of stage T1–T2 pyriform sinus carcinoma is rarely invaded. It is the best indication for this surgical approach. In addition, the paraglottic space approach can be used if the T3–T4 lesion does not involve the paraglottic space, because most cases of the vocal cord fixation is caused by tumour compression and not by tumour invasion of the paraglottic space [7]. For the carcinoma of the lateral wall of the piriform sinus, the tumour rarely invades the larynx because of its anatomical position. The approach through the paraglottic space can fully separate the hypopharynx and larynx, that is, the entire tumour can be directly exposed from the ventral side. The surgical field of view is wide, and the tumour can be accurately removed. For the primary tumour in the medial wall of the pyriform sinus, the transglottic approach can firstly complete the resection of the deep cutting edge of the tumour when entering the pharyngeal cavity, then separate the tumour from the larynx by pulling the thyroid cartilage plate outward and remove the tumour under direct vision. Preoperative cervical enhanced CT and electronic laryngoscopic examination can effectively determine the presence or absence of paraglottic space and laryngeal cartilage involvement. If the paraglottic space is involved, in the actual surgical operation, we can first enter through the paraglottic space approach, separate the hypopharynx and larynx and then combine the lateral pharyngeal approach, and observe the scope of tumour invasion in multiple planes. Supraglottic hemilaryngopharyngectomy, partial pharyngectomy or total laryngectomy is performed according to the actual extent of tumour invasion.

In addition, the incidence of pharyngeal fistula in this study was 4.3%, which was considerably lower than those in other studies[6,8]. As mentioned above, the paraglottic space approach can retain more normal hypopharyngeal mucosa, dissociate the pharynx from the larynx, effectively reduce the suture tension during pharyngeal reconstruction and prevent mucosal avulsion during pharyngeal movement. In addition, the lifting of the uninvaded lateral thyroid lobe to strengthen the pharyngeal wall is another main reason to reduce

the occurrence of pharyngeal fistula. The lateral thyroid lobe has good blood circulation and large tissue volume, which can be used as the strengthening plane of the new pharyngeal cavity.

## Conclusion

In summary, the paraglottic space approach is a novel surgical approach, which can better expose the tumour. On the premise of ensuring a safe tumour resection margin, this approach has obvious advantages in preserving laryngeal function and reducing the serious postoperative complications of pyriform sinus carcinoma. It is beneficial in improving the quality of life of patients after surgery. This surgical approach can be applied in patients with lesions that do not involve the paraglottic space. N stage is an independent risk factor for postoperative survival. This study still has the deficiency of a relatively small sample size. Nonetheless, the resection method for primary postcricoid carcinoma and posterior pharyngeal wall carcinoma via the paraglottic space approach is worth further exploring and trying.

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