# Larynx-preserving limited resection with total thoracic esophagectomy and gastric pull-up reconstruction: A promising treatment for selected cervical esophageal squamous cell carcinoma

*Wu-ping Wang#, Jie Ma#, Qiang Lu#, Yong Han, Xiao-fei Li, Tao Jiang, Jin-bo Zhao*

*Department of Thoracic Surgery, The Second Affiliated Hospital of AFMU, Air Force Medical University, Xi'an, China*

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## ABSTRACT

***Background/Aims:*** *There is no consensus on treatment for cervical esophageal squamous cell carcinoma (ESCC). Our aim is to evaluate the feasibility and outcome of larynx-preserving limited resection with total thoracic esophagectomy and gastric pull-up reconstruction for the treatment of cervical ESCC without tumor involvement of the larynx and hypopharynx.*

***Materials and Methods:*** *Retrospective analysis of patients with cervical ESCC who underwent R0 surgical resection from 2006 to 2011 in our center was performed. Kaplan-Meier method was used to calculate the survival time for patients.*

***Results:*** *In total, 74 cervical ESCC patients were enrolled in the study. The mortality rate in 30 days was 8.1%, the total complication rate (at least one) was 47.3%, anastomosis leakage occurrence was 37.8%, mechanical ventilation ratewas12.2%, the rate of normal oral diet within 15 days was 71.6%, and the anastomosis recurrence rate in follow-up was 8.1%. Detailed analysis showed that the anastomosis leakage, pulmonary infection, laryngeal recurrent nerve injury, and chylothorax were the most common complications in surgical patients. Finally, the survival data showed that the median survival time was 31.83 months (95% CI=12.39-51.28 months) and the 3-year and 5-year survival rates were 49.1% and 35.5%, respectively.*

***Conclusion:*** *Larynx-preserving limited resection with total thoracic esophagectomy and gastric pull-up reconstruction might be a feasible and effective surgical alternative for the cervical ESCC patients whose tumor does not involve the larynx and hypopharynx.*

***Keywords:*** *Cervical ESCC, larynx-preservation, surgery, prognosis, overall survival*

## INTRODUCTION

Carcinoma of the cervical esophagus is a rare malignancy, which accounts for less than 5% of the total cases of esophageal cancer (1, 2). The treatment of this disease is a big challenge for clinicians. To date, there is no consensus on treatment for this rare disease, and there is also no ongoing prospective randomized controlled study to explore a better treatment strategy (3). At present, various options, including definitive chemoradiotherapy (CRT), neoadjuvant therapy followed by surgical resection, surgery alone, or surgical resection followed by adjuvant therapy are available (4-9).

From the perspective of preservation of the laryngeal and pharyngeal functions (5, 8) and based on early trials for the head and neck squamous cell carcinoma patients and esophageal cancer patients (10, 11), definitive CRT has been recommended as the initial treatment for cervical esophageal squamous cell carcinoma (ESCC) in the United states (3, 12). However, the 5-year survival rate after definitive CRT is poor, and a few of patients finally still need salvage surgery owing to failure of local tumor control (13-17). On the contrary, surgery alone or surgical resection accompanied with multi-disciplinary therapies, to some extent, can lead to relatively good long-term survival rates (9, 18). Therefore, selected patients with cervical ESCC in Asian, Europe, and even in America, were referred for surgical treatment (3, 5-9, 18, 19).

To our knowledge, surgical resection of cervical ESCC is very challenging, and there is no standard technique recommended in practice. Some head and neck surgeons perform radical resection including total cervical esophagectomy and laryngo pharyngectomy, even though the larynx and hypopharynx are not invaded in most cases (13, 18, 19). However, the bad quality of life (QOL) after non larynx-preserving surgery as well as the non-significant improvement in the patients' survival

*#These authors contributed equally to the study*

*Corresponding Author:* ***Jin-bo Zhao; zhaojinbo@aliyun.com; Xiao-fei Li; lxfchest@fmmu.edu.cn***

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rate led the surgeons to explore the larynx-preserving surgeries (5, 8, 18). One promising report indicated that a limited tumor resection in neck followed by free jejunal graft interposition could have good surgical results (5), but this procedure needs microscopical vascular anastomosis technique and was only applied to those with tumor not extended into the thoracic. In addition, the thoracic lymph node was not resected in that condition. Therefore, there is a need of simple and effective surgical procedures.

In our institution, tumor resection with total thoracic esophagectomy and gastric pull-up reconstruction in neck is a common procedure used for the treatment of upper esophageal cancer, and according to our experience, most cervical ESCC patients have a good outcome after receiving larynx preserving R0 (margin negative) tumor resection, although the "5 cm safety distance" is not achieved theoretically in those surgical patients. We conducted this retrospective study to systematically evaluate the efficiency of this procedure for cervical ESCC patients without tumor involvement of the larynx and hypo pharynx.

## MATERIALS AND METHODS

### Patients' Enrollment and Surgical Intervention

We enrolled the patients who had been consecutively diagnosed with cervical ESCC and underwent tumor resection with total thoracic esophagectomy and gastric pull-up reconstruction in neck from 2006 to 2011 in our Department. All the patients' tumor was staged according to the pathological tumor/node/metastasis (p-TNM) classification (7th edition) of the international union against cancer. This study was also approved by the ethics committee for clinical research of our hospital (TDLL-KY-202012-02).

In this study, the cervical ESCC patients were defined as those with the tumor upper border located between cricopharyngeus and suprasternal notch level, which was confirmed by both esophagoscopy and barium contrast study. In all, the inclusion criteria and exclusion criteria are as follows: Patients with cervical ESCC with involvement of the larynx and hypopharynx was excluded, R0 upper margin resection that was confirmed by intraoperative frozen and postoperative pathology should be achieved in all patients, the tumor upper border should have a distance of ≥1 cm and ≤5 cm from cricopharyngeus; those with distance less than 1cm were excluded considering the difficulty in anastomosis.

**MAIN POINTS**

- *There is no consensus on treatment for cervical esophageal squamous cell carcinoma (ESCC), and larynx-preserving limited resection with total thoracic esophagectomy and gastric pull-up reconstruction was feasible for selected cervical ESCC patients.*

Patients with cervical ESCC had undergone similar surgical intervention with the upper thoracic ESCC, total thoracic esophagectomy, and gastric pull-up with anastomosis in neck, a routine which is recognized as simple and valid surgical procedure recommended for upper thoracic ESCC patients worldwide. The only difference in our study was that the "5 cm safety distance (the distance from tumor upper border to the final tumor upper resection margin ≥ 5cm)" was not achieved theoretically in the cervical ESCC patients when receiving this surgical procedure, which was defined as larynx-preserving limited resection in this study. The overall survival (OS), postoperative parameters, and complications were analyzed in the enrolled cervical ESCC patients.

### Peri-operative Intervention and Follow-up

Before the surgery, all patients received routine examination, including neck ultrasound or computed tomography (CT) scan, chest CT, abdominal ultrasound or CT, brain CT or Magnetic Resonance Imaging (MRI), Emission Computed Tomography (ECT)or Positron Emission Tomography CT (PET-CT) scan, and cardiopulmonary function and hepatorenal function tests to confirm that there was no contraindication for the surgery. The bronchoscopy was performed for every patient to confirm that the trachea was not invaded. After operation, all the patients were given combined enteral or parenteral nutrition support and prophylactic antibiotics treatment to ensure a smooth postoperative recovery. The post-discharge follow-up was performed as follows in all patients enrolled in the study: 1 month after the first discharge, every 6 months in the first 3 years, and annually thereafter. Each follow-up included a complete examination, including basic serum chemistry, barium contrast study, and ultrasonography of the abdominal and cervical regions. CT scans of the neck and thorax and endoscopy were performed after the completion of treatment and then every 6 months.

### Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 13.0 (SPSS, Chicago, IL,

**Table 1.** Basic characteristics of the patients.

| | Number (n) | Percentage (%) |
|---|---|---|
| Sex | | |
| Male | 47 | 63.5 |
| Female | 27 | 36.5 |
| Age | | |
| ≤ 60 years | 32 | 43.2 |
| > 60 years | 42 | 56.8 |
| Smoking | | |
| Yes | 28 | 37.8 |
| no | 46 | 62.2 |
| Alcohol drink | | |
| Yes | 5 | 6.8 |
| no | 69 | 93.2 |
| Tumor length | | |
| ≤ 5CM | 47 | 63.5 |
| > 5CM | 27 | 36.5 |
| Surgical road | | |
| Left (thoracic+neck) | 57 | 77 |
| VATS | 11 | 15 |
| Three incisions | 6 | 8 |
| Differentiation | | |
| high | 9 | 12.2 |
| middle | 47 | 63.5 |
| low | 18 | 24.3 |
| p-TNM stage | | |
| stage I-II | 54 | 73 |
| stage III-IV | 20 | 27 |
| Adjuvant chemo-therapy | | |
| Yes | 32 | 43.2 |
| no | 42 | 56.8 |
| Adjuvant radio-therapy | | |
| Yes | 9 | 12.2 |
| no | 65 | 87.8 |

USA). All data are expressed as the mean±SD. Overall survival was calculated from the date of surgery to the occurrence of death or to the last known follow-update. Actual survival was calculated by the Kaplan-Meier method and evaluated statistically by the log-rank test.

**Table 2.** Postoperative parameters of those patients.

| | Number (n) | Percentage (%) |
|---|---|---|
| Mortality in 30 days | | |
| Yes | 6 | 8.1 |
| no | 68 | 91.9 |
| At least one complication | | |
| Yes | 35 | 47.3 |
| no | 39 | 52.7 |
| Multiple complications | | |
| Yes | 13 | 17.6 |
| no | 61 | 82.4 |
| Anastomosis leakage | | |
| Yes | 28 | 37.8 |
| no | 46 | 62.2 |
| Mechanical ventilation | | |
| Yes | 9 | 12.2 |
| no | 65 | 87.8 |
| Normal oral diet within 15 days | | |
| Yes | 53 | 71.6 |
| no | 21 | 28.4 |
| Anastomosis recurrence | | |
| Yes | 6 | 8.1 |
| no | 68 | 91.9 |

## *RESULTS*

### *Patient Characteristics*

In total, 74 cervical ESCC patients were finally enrolled in the study. None of the patients received any preoperative treatment. Table 1 presents the baseline characteristics of the patients.

### *Postoperative Parameters and Complications*

To evaluate the safety of the surgical procedure indicated for cervical esophageal cancer patients, we analyzed a series of surgery-related parameters and complications described below. As shown in Table 2, the mortality rate in 30 days was 8.1%, the total complication rate (at least one) was 47.3%, the anastomosis leakage occurrence was 37.8%, the mechanical ventilation rate was 12.2%, the rate of normal oral diet within 15 days was 71.6%, and the anastomosis recurrence rate in follow-up was 8.1%. In addition, the rate of patient with multiple complica-

**Table 3.** Detailed Complications of the cervical ESCC patients

| | Number (n) | percentage (%) |
|---|---|---|
| Anastomosis leakage | 28 | 37.8 |
| Pulmonary infection | 8 | 10.8 |
| Laryngeal recurrent nerve injury | 4 | 5.4 |
| Anastomotic stenosis | 1 | 1.3 |
| Chylothorax | 4 | 5.4 |
| Infection or rupture of in-cision | 1 | 1.3 |
| Esophageal tracheal fistu-la | 1 | 1.3 |
| Pulmonary embolism | 0 | 0 |
| Empyema | 1 | 1.3 |
| Active bleeding | 0 | 0 |
| Aspiration | 1 | 1.3 |
| Total compliations num-ber | 49 | |

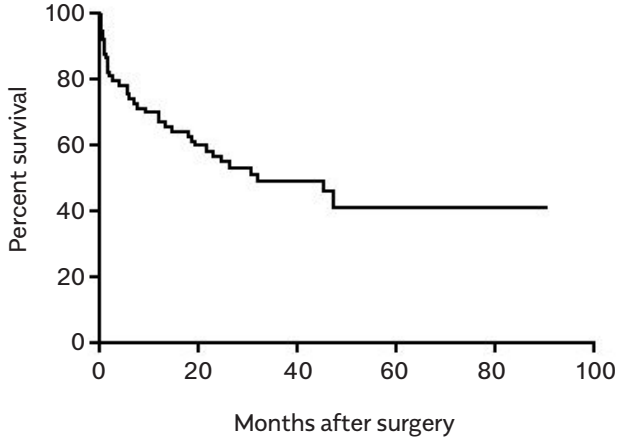


**Figure 1.** Survival analysis for all cervical ESCC patients (n=74)

tions (at least two) was 17.6%. Detailed complications are listed in Table 3, in which the anastomosis leakage, pulmonary infection, laryngeal recurrent nerve injury, and chylothorax seem to be the most common complications in all patients.

### *Survival Analysis*

In order to investigate the efficacy of the surgical procedure indicated for cervical esophageal cancer patients, the survival data of the patients were calculated by Kaplan-Meier method. The results showed that the median survival time of all cervical ESCC patients (n=74) was 31.83 months (95% CI=12.39 - 51.28 months) (Figure 1), and the 3-year and 5-year survival rate were49.1% and 35.5%, respectively.

## *DISCUSSION*

The treatment for cervical ESCC is a big challenge for clinicians. Based on the practice of our institution, the chemoradiation therapy (CRT) was recommended for those with tumors invading the surrounding tissue or the larynx and hypopharynx and for those whose tumor upper border had a distance of less than 1cm from cricopharyngeus. Otherwise, the surgical resection was performed. Neoadjuvant therapy was not given in our center, whereas the adjuvant therapy after surgery was only recommended for patients with late stage or non-R0 resection. Surgical resection of cervical ESCC is extremely challenging. In china, most cervical ESCC patients, especially those with tumor invasion of the larynx and hypopharynx, are commonly treated by head and neck surgeons through laryngo pharyngectomy and total cervical esophagectomy, which has been reported to be associated with poor QOL after larynx resection in a series of studies (7, 8, 9, 13, 18, 19). Due to professional limitations, this traditional surgery always needs the participation and cooperation of abdominal surgical teams to ensure a smooth digestive tract reconstruction (20, 21). In addition, thoracic esophagectomy and lymphadenectomy, which are difficult to perform techniques for head and neck surgeons, are indispensable when cervical ESCC extends into the thoracic esophagus. In existing literature, Ott et al. have reported that a limited resection of cervical ESCC with larynx preservation followed by free jejunal graft interposition could have a good outcome (5). However, this procedure was complex in microvascular anastomosis and was applied only for those patients with tumor limited in the cervical esophagus (5, 8). In our department, cervical ESCC patients without tumor involvement of the larynx and hypopharynx account for the majority of cervical ESCC patients, and most of them presented with tumor lesion extending into the thoracic esophagus (for example, in this study, 94.6% (70/74) patients are those with tumor extending into the thoracic esophagus). Therefore, larynx-preserved tumor resection with total thoracic esophagectomy and gastric pull-up reconstruction may be a potentially suitable and simple alternative for cervical ESCC patients whose tumor extending into the thoracic esophagus, but without tumor involvement of the larynx and hypopharynx. This retrospective analysis has demonstrated the feasibility and outcome of this approach indicated for particularly those cervical ESCC patients.

The possible higher anastomotic recurrence rate, such as the one we investigated in the study, when performing the larynx-preserved surgery should be taken into consideration. Although R0 tumor upper margin resection was confirmed by operative frozen and postoperative pathology, the "5cmsafety distance" was not achieved theoretically in cervical ESCC patients. However, when compared with upper thoracic ESCC patients, in whom the safety distance was unambiguously achieved while performing a similar surgical intervention, the results showed no difference in recurrence rate between them (8.11% vs 7.08%, p=0.784), as shown in Supplementary Table 1. These data strongly supported that the limited tumor resection in this study did not increase the anastomotic recurrence rate and indicated that the non-safety distance resection was feasible.

When we analyzed the postoperative parameters and complications of the cervical ESCC group patients, we found that cervical ESCC patients presented with a total complication rate of 47.3%, and cervical anastomosis leakage was the most common surgical complication, with a rate of 37.8%, and the mortality in 30 days (8.1%) was not low in our study. However, to our knowledge, the pervious reported rate on total complication, cervical anastomosis leakage, and hospital mortality in surgical cervical ESCC patients ranged from 11% to 74.3% (5, 22, 23), 5.5% to 43% (6, 20, 24), and 4.8% to 33.3% (22, 25-29), respectively. Compared with these data, the total complication rate, cervical anastomosis leakage rate, and mortality rate in 30 days associated with larynx-preserving operation in our study were acceptable. When compared with the upper thoracic ESCC patients, the results showed no difference in postoperative parameters and complications between cervical ESCC and upper thoracic ESCC patients (all p>0.05, as shown in Supplementary Table 1), which indicated that the higher tumor location, such as the tumor located in cervical esophagus, did not affected significantly the risk of the surgery.

Considering the outcome of the surgical approach, we analyze the patients' survival. The results showed that cervical patients could have a 5-year survival rate of 41.2%, which was superior to or comparable with chemoradiation therapy (CTRT), or concurrent CTRT indicated for cervical ESCC patients, in which the reported 5 years OS ranges from 18.6% to 40% (14, 25, 30-32). Our data was also comparable with the results of previous studies on surgical intervention for cervical ESCC patients, where the 5-year survival rate was reported to be 16.6% to 47% (5, 17, 22, 23, 25, 33). Even so, our patients should have presented with a higher 5-year survival rate if some bad condition is avoided. For example, in this study, left thoracic-incision surgery was performed on majority of cervical ESCC patients (77%), by which the thoracic lymph node could not be systemically dissected and resulted in a lower survival time when compared with the three-field lymph node dissection surgery and others. In addition, multidisciplinary therapies were not performed well in our study, such as the lack of neoadjuvant therapy and irregular adjuvant therapy (no evidence-supported chemotherapy and dose-insufficient radiotherapy), which leads to unimproved survival too. Finally, to further evaluate the efficiency of this surgical approach for cervical ESCC, we compared the survival time of cervical ESCC patients with that of upper thoracic ESCC patients in different conditions by both propensity un-matched analysis and matched analysis. The results showed that there were no significant difference in survival time between them (p>0.05, Supplementary Figure 1), which indicated that larynx-preserving limited resection with total thoracic esophagectomy and gastric pull-up reconstruction for treatment of cervical ESCC without involvement of the larynx and hypopharynx could achieve the same clinical outcome in upper thoracic ESCC patients. In all, the survival time of our patients was acceptable and improvable. Thus, we believe that our surgical strategy is a promising treatment strategy for cervical ESCC patients.

To our knowledge, our cohort was a relative larger series in which surgical approaches indicated for the selected cervical ESCC patients were investigated (8,9,18-22,24-29), and the results seem to be acceptable. However, there are some shortcomings of the study. For example, the study was a retrospective analysis, and thus, we cannot compare it with the already existing surgical approaches used for cervical ESCC and with concurrent chemoradiotherapy (CTRT) for cervical esophageal cancer to evaluate the advantages of our surgical method in the target population. Therefore, we propose a well-designed multicenter prospective randomized controlled trial to further investigate the safety and efficacy of the surgical approach indicated for cervical ESCC patients without tumor involvement of the larynx and hypopharynx and to identify the target population which may maximize the benefits from this surgical treatment.

In conclusion, the larynx-preserving limited resection with total thoracic esophagectomy and gastric pull-up reconstruction used for treatment of cervical ESCC without involvement of the larynx and hypopharynx seemed to be a promising surgical alternative for selected cervical

ESCC patients. However, a well-designed clinical randomized control trial is still needed to further evaluate the efficiency of the present surgical approach for the targeted patients.

***Ethics Committee Approval:*** Ethics Committee Approval has received for this study from the Ethics Committee of the Second Affiliated Hospital of AFMU, Air Force Medical University (TDLL-KY-202012-02)

***Informed Consent:*** Informed consent is not necessary due to the retrospective nature of this study.

***Peer-review:*** Externally peer-reviewed.

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***Conflict of Interest:*** The authors have no conflict of interest to declare.

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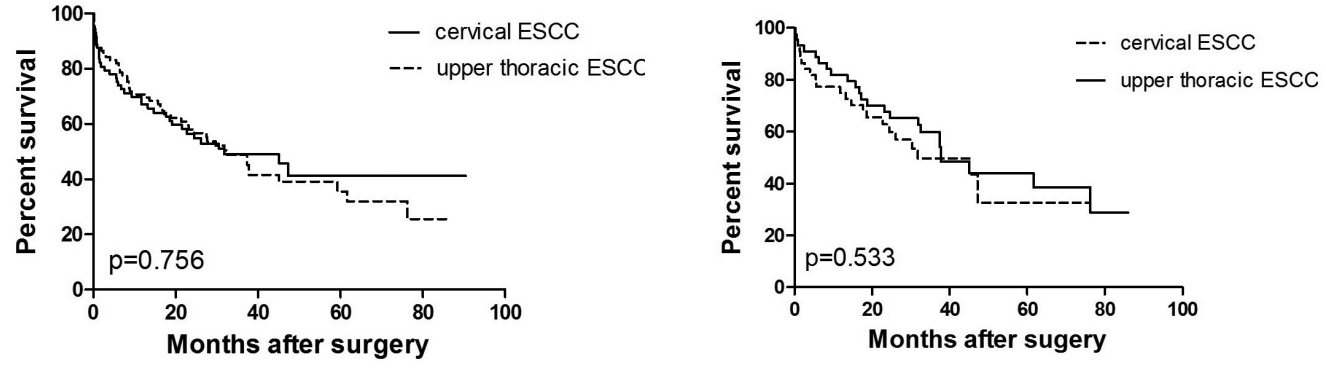
**Supplementary Table 1**

| | Groups before propensity matching | | | |
|---|---|---|---|---|
| Postoperative parameters | Patients number | Cervical ESCC group (n=74) | Upper thoracic ESCC group (n=113) | p |
| Operation time (min) | | 248.23±79.193 | 253.72±75.984 | 0.635 |
| Blood lose (mL) | | 486.49±263.836 | 488.76±301.426 | 0.995 |
| Mortality in 30 days | | | | 1.000 |
| Yes | 15 | 6 | 9 | |
| no | 172 | 68 | 104 | |
| At least one complication | | | | 0.455 |
| Yes | 82 | 35 | 47 | |
| no | 105 | 39 | 66 | |
| Multiple complications | | | | 0.530 |
| Yes | 28 | 13 | 15 | |
| no | 159 | 61 | 98 | |
| Anastomosis leakage | | | | 0.341 |
| Yes | 62 | 28 | 34 | |
| no | 125 | 46 | 79 | |
| Mechanical ventilation | | | | 1.000 |
| Yes | 24 | 9 | 15 | |
| no | 163 | 65 | 98 | |
| Normal oral diet within 15 days | | | | 0.746 |
| Yes | 131 | 53 | 78 | |
| no | 56 | 21 | 35 | |
| Anastomosis recurrence | | | | 0.784 |
| Yes | 14 | 6 | 8 | |
| no | 173 | 68 | 105 | |




**Supplementary Figure 1.** Left: Survival comparison between cervical ESCC patients (n=74) and upper thoracic ESCC patients (n=113) before propensity matching: right Survival comparison between cervical ESCC patients (n=44) and upper thoracic ESCC patients (n=44) after propensity matching.