Cohort Study

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Effect of cervical paraesophageal lymph node metastasis versus supraclavicular lymph node metastasis on the overall survival of patients with thoracic esophageal squamous cell carcinoma: an observational study

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Background: Esophageal cancer (EC) is a major global health burden, with a particularly high incidence in East Asia. The authors aimed to investigate the effect of metastasis in cervical paraesophageal lymph nodes (station 101) and supraclavicular lymph nodes (station 104) on the survival of patients who underwent esophagectomy for esophageal squamous cell carcinoma (ESCC).

Materials and Methods: Data were obtained from the database of the authors' hospital. The authors retrospectively analyzed the patients with EC who underwent esophagectomy from January 2010 to December 2017. These patients were allocated into two groups based on the presence of lymph node metastasis (LNM) in the cervical paraesophageal or supraclavicular regions. Clinical outcomes and survival data were compared using the TNM staging system of the 8th edition of the American Joint Committee on Cancer (AJCC).

Results: After a median follow-up of 62.1 months, 122 patients with LNM in the supraclavicular region were included in the study. Among these patients, 53 showed cervical paraesophageal LNM and an overall survival (OS) of 19.9 months [95% confidence interval (CI): 16.3–23.5]. In contrast, 69 patients showed supraclavicular LNM with an OS of 34.9 months (95% CI 25.7–44.1). The OS rates at 1, 3, and 5 years were 77%, 29%, and 21%, respectively, for patients with cervical paraesophageal LNM. Moreover, patients with supraclavicular LNM demonstrated OS rates of 88%, 48%, and 34%, respectively [Hazard ratio (HR): 0.634, 95% CI: 0.402–1.000, $P = 0.042$].

Conclusions: Patients with ESCC with cervical paraesophageal LNM had significantly worse OS than those with supraclavicular LNM. This study underscores the importance of accurately identifying and managing ESCC with cervical paraesophageal LNM, as it may require more tailored and aggressive treatment strategies to prolong patient survival.

Keywords: cervical paraesophageal lymph node metastasis, esophagectomy, lymphadenectomy, esophageal squamous cell carcinoma, supraclavicular lymph node metastasis

Introduction

Esophageal cancer (EC) is a prominent health concern worldwide, especially in East Asia[1,2]. The management of esophageal squamous cell carcinoma (ESCC) involves three established therapeutic modalities: esophagectomy, chemotherapy, and radiotherapy[3–5]. Although esophagectomy is the most common treatment approach for EC, its efficacy is limited in patients with metastatic tumors[6,7]. Therefore, early diagnosis and timely treatment play important roles in the management of patients with EC[6,7]. Chemotherapy is a therapeutic modality that kills tumor cells through the injection or intravenous infusion of one or more agents into the tumor tissues[8]. Currently, the main

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agents for chemotherapy in EC include cisplatin, paclitaxel, and irinotecan, among other pharmacological options[8]. Radiation therapy uses radioactive emission to eliminate malignant cells[9]. Emerging approaches, such as targeted therapy and immunotherapy, are currently under active investigation in clinical trials for the treatment of EC[10–12]. Despite notable progress in diagnostic and therapeutic modalities, the prognosis for patients with thoracic ESCC remains unfavorable, mainly due to the high tendency for metastasis and local disease recurrence[3–5].

In cases of resectable EC, a comprehensive treatment regimen based on surgery is the primary treatment approach[13–15]. Lymph node metastasis (LNM) is a critical factor in determining the prognosis of individuals with thoracic ESCC, reflecting the degree of disease spread and the potential for systemic dissemination[16–18]. Lymphadenectomy is crucial in the surgical procedure of esophagectomy[19]. In 1990, Isono *et al.*[18] proposed the concept of dissection of cervical lymph nodes (LNs) during esophagectomy. According to the guidelines established by the Japan Esophageal Society (JES), cervical paraesophageal (station 101) LNM and supraclavicular (station 104) LNM are indicative of locally advanced disease[7,19]. However, only supraclavicular LNM is classified as distant metastasis and categorized as M1 based on the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC)[20]. Currently, there is a consensus that cervical paraesophageal LNM and supraclavicular LNM should be collectively regarded as LNM of the supraclavicular region. However, Japanese scholars have recently undertaken a nationwide multicenter JCOG2013 study to further investigate the significance of 104-station LN dissection in the current clinical practice. Although the results of this study have not been publicly available, it is evident that the removal of cervical LNs is one of the focuses of lymphadenectomy among esophageal surgeons worldwide[21].

Although numerous studies have investigated the impact of LNM on the survival of patients with thoracic ESCC, there is a paucity of long-term survival analyses directly comparing the effect of cervical paraesophageal LNM and supraclavicular LNM. Understanding the differences in overall survival (OS) holds significant importance in optimizing treatment strategies and enhancing patient outcomes in the context of ESCC. Therefore, this study aims to conduct a comprehensive long-term survival analysis to compare the OS of thoracic ESCC patients with LNM at station 101 and those with LNM at station 104. By elucidating the relative impact of these two patterns of metastasis, we seek to provide valuable insights that can assist clinicians in tailoring personalized treatment approaches and ultimately improve the prognosis for patients with thoracic ESCC.

Materials and methods

Data were obtained from the database of our hospital. We conducted a retrospective analysis of ESCC patients between January 2010 and December 2017. This study was approved by the Ethics Committee of Medical Research and Medical New Technologies of our hospital (details blind for peer review). The reporting of this study complies with STROCSS guidelines[22].

Demographic and pathologic data, including gender, age, pathological T stage, pathological N stage, 8th tumor-node-metastasis (TNM) stage, tumor location, tumor grade, lymphovascular invasion, perineural invasion, LNM, cervical paraesophageal LNM, supraclavicular LNM, and radical resection, were collected from our database. A retrospective analysis was conducted on a cohort of patients diagnosed with ESCC from January 2010 to December 2017. These patients underwent esophagectomy, which was performed using a right transthoracic approach and included the application of three-field lymphadenectomy. The inclusion criteria were as follows: (1) patients who had undergone esophagectomy and (2) patients who exhibited LNM in the supraclavicular region. On the other hand, the criteria for excluding participants from the study consisted of (1) tumor location outside the thoracic region, (2) pathological examination results confirming the presence of non-squamous cell carcinoma, (3) patients with both cervical paraesophageal LNM and supraclavicular LNM, or (4) those with missing required data (Fig. 1). The staging of ESCC adhered to the guidelines provided by the 8th edition of the UICC/AJCC TNM staging system. Patients were grouped according to their pathological findings, where patients with paraesophageal LNM were assigned to the 101 group, while those with supraclavicular LNM were assigned to the 104 group. Patients underwent regular follow-up examinations at intervals of 3 months for the first 2 years, after which the follow-up frequency

HIGHLIGHTS

- Esophageal squamous cell carcinoma (ESCC) is the main occurring subtype in China.
- Lymph node metastasis (LNM) in cervical paraesophageal or supraclavicular region disputes over N stage and M stage.
- Two-field lymphadenectomy was the main surgical treatment model.
- LNM in cervical paraesophageal or supraclavicular region is an independent prognostic factor for overall survival.

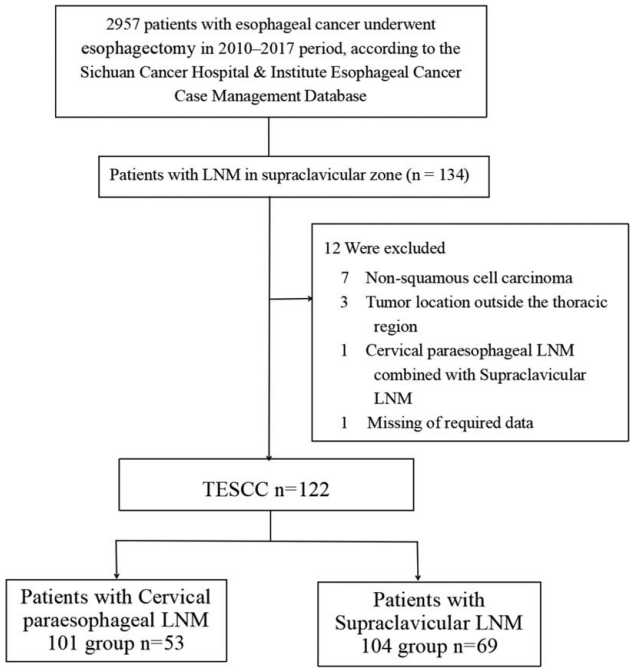

Figure 1. CONSORT diagram showing the process of patient selection. LNM, lymph node metastasis; TESCC, thoracic esophageal squamous cell carcinoma.

was adjusted to every 6 months for the remaining 3–5 years. OS was calculated from the month and year of surgery until the time of death or the last follow-up in March 2021.

Theory/calculation

Statistical analysis

Categorical variables were presented as percentages. Data were analyzed using the χ^2 test or Fisher's exact test. Risk factors for independent OS were identified using both univariate and multivariate logistic regression analyses. The analysis involved the calculation of hazard ratios (HRs) and 95% confidence intervals (CIs). Cox proportional hazards regression models were used to assess the impact of all baseline covariates on the survival outcome. Kaplan–Meier curves were constructed using the GraphPad Prism 9 software, and log-rank tests were used to analyze the median values at specific time points within the 95% CIs. A value of $P < 0.05$ was considered statistically significant. SPSS software version 23.0 (Chicago, Illinois, USA) was used for all data analyses.

Results

Patient characteristics

The data of 122 patients diagnosed with supraclavicular LNM from January 2010 to December 2017 were analyzed in this study. The study flowchart is presented in Figure 1, which outlines the inclusion of 53 participants with paraesophageal LNM and 69 with supraclavicular LNM. The clinicopathological and pathological characteristics of the enrolled patients are presented in Table 1. The comparative analysis of two groups of patients showed significant differences only in tumor location, abdominal surgery, and treatment modality (Table 1). However, when assessing the impact of these three factors on OS through both the univariate and multivariate Cox regression models, no statistically significant associations were observed (Table 2).

Table 1

Characteristics of the patients.

Characteristic	Patients (122) 101 metastasis (53)	104 metastasis (69)	*P*
Sex			0.643
Male	44 (83.0%)	55 (79.7%)	
Female	9 (17.0%)	14 (20.3%)	
Age, years			0.350
Median (range)			
< 75	52 (98.1%)	64 (92.8%)	
≥ 75	1 (1.9%)	5 (7.2%)	
Pathologic differentiation grade			0.429
Well G1	6 (11.3%)	9 (13.0%)	
Moderate G2	14 (26.4%)	25 (36.2%)	
Poor or undifferentiated G3	33 (62.3%)	35 (50.7%)	
Lymphovascular invasion			0.144
Yes	16 (30.2%)	13 (18.8%)	
No	37 (69.8%)	56 (81.2%)	
Nerve invasion			0.707
Yes	9 (17.0%)	10 (14.5%)	
No	44 (83.0%)	59 (85.5%)	
Tumor location			0.006
Upper	19 (35.8%)	41 (59.4%)	
Middle	28 (52.8%)	27 (39.1%)	
Lower	6 (11.3%)	1 (1.4%)	
Pathological T stage			0.405
T1	4 (7.5%)	3 (4.3%)	
T2	10 (18.9%)	10 (14.5%)	
T3	30 (56.6%)	49 (71.0%)	
T4	9 (17.0%)	7 (10.1%)	
Pathological N stage			0.880
N1	16 (30.2%)	21 (30.4%)	
N2	18 (34.0%)	26 (37.7%)	
N3	19 (35.8%)	22 (31.9%)	
8th TNM Stage			1.000
IV	53 (100.0%)	69 (100.0%)	
Thoracic surgery			0.085
MIE, *n* (%)	15 (28.3%)	30 (43.5%)	
OE, *n* (%)	38 (71.7%)	39 (56.5%)	
Abdominal surgery			0.008
MIE, *n* (%)	11 (20.8%)	30 (43.5%)	
OE, *n* (%)	42 (79.2%)	39 (56.5%)	
Clinical treatment modality			0.350
Surgery alone	52 (98.1%)	64 (92.8%)	
Surgery plus postoperative CT or RT/CRT	1 (1.9%)	5 (7.2%)	

CRT, chemoradiotherapy; CT, chemotherapy; MIE, minimally invasive esophagectomy; OE, open esophagectomy; RT, radiotherapy.

Overall survival

After a median follow-up of 62.1 months, 122 patients with LNM in the supraclavicular region were included. Among these patients, 53 had cervical paraesophageal LNM, while 69 had supraclavicular LNM. The median OS of the patients with cervical paraesophageal LNM was 19.9 months (95% CI: 16.3–23.5), while that of the patients with supraclavicular LNM was 34.9 months (95% CI 25.7–44.1). The OS rates at 1, 3, and 5 years for patients with cervical paraesophageal LNM were 77%, 29%, and 21%, respectively, while those for the patients with supraclavicular LNM were 88%, 48%, and 34%, respectively (Fig. 2). None of our patients received neoadjuvant therapy, and only six patients received postoperative treatment. We did not provide a detailed grouping for them. Regarding early postoperative deaths, Group 101 and Group 104 each had one patient who died within the first month. However, due to the retrospective nature of our study, we failed to determine the cause of death.

Risk factors

Univariate analysis indicated that several factors had a significant impact on the 5-year OS after esophagectomy, including sex ($P = 0.016$), perineural invasion ($P = 0.017$), pathological N stage ($P = 0.048$), and supraclavicular LNM ($P = 0.043$), as indicated in Table 2. The subsequent multivariate analysis revealed that only supraclavicular LNM ($P = 0.035$) significantly affected the 5-year OS after esophagectomy (Table 2).

Discussion

This study clarified the clinical significance of lymphadenectomy in metastasis at station 101 and station 104. There were no statistically significant differences in the demographic characteristics between the two groups, except for the tumor location, abdominal surgery, and clinical treatment modality. These factors

Table 2

Univariate and multivariate Cox regression analyses of factors affecting patient survival.

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sex						
Male	Ref.		Ref.			
Female	0.441	(0.227–0.857)	0.016	0.515	(0.259–1.026)	0.059
Age, years						
<75	Ref.					
≥75	1.521	(0.554–4.173)	0.416			
Pathologic differentiation grade			0.350			
Well G1	Ref.		Ref.			
Moderate G2	1.105	(0.531–2.297)	0.789			
Poor or undifferentiated G3	0.776	(0.389–1.549)	0.472			
Lymphovascular invasion						
Yes		Ref.			Ref.	
No	0.721	(0.431–1.203)	0.210			
Nerve invasion						
Yes		Ref.			Ref.	
No	0.491	(0.273–0.883)	0.017	0.601	(0.325–1.113)	0.105
Tumor location			0.122			
Upper	Ref.					
Middle	1.461	(0.917–2.328)	0.111			
Lower	2.125	(0.886–5.094)	0.091			
Pathological T stage			0.334			
T1		Ref.			Ref.	
T2	0.771	(0.263–2.260)	0.636			
T3	1.182	(0.471–2.967)	0.721			
T4	1.708	(0.590–4.943)	0.323			
Pathological N stage			0.048			0.216
N1		Ref.			Ref.	
N2	1.958	(1.094–3.506)	0.024	1.649	(0.893–3.045)	0.110
N3	1.929	(1.069–3.480)	0.029	1.628	(0.883–3.000)	0.118
Thoracic surgery						
MIE		Ref.				
OE	1.074	(0.851–1.354)	0.549			
Abdominal surgery						
MIE		Ref.				
OE	1.104	(0.867–1.405)	0.422			
Clinical treatment modality						
Surgery alone		Ref.				
Surgery plus postoperative CT or RT/CRT	1.106	(0.700–1.747)	0.667			
101/104						
101		Ref.			Ref.	
104	0.632	(0.404–0.986)	0.043	0.616	(0.392–0.967)	0.035

CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; MIE, minimally invasive esophagectomy; OE, open esophagectomy; RT, radiotherapy.

did not have a significant effect on the 5-year OS after esophagectomy.

According to the JES standard, tumor location and LNM are essential factors when determining the N stage classification[7]. Tachimori *et al*. proposed that the zones of LN metastasis and tumor locations had different efficacy indexes (EI) in their outcomes; this was further verified in the Chinese data[19,23,24]. Their study has revealed that the 5-year OS rate for patients with LNM in the supraclavicular region was 27.7–60.7%. Additionally, the T stage and location were identified as important factors affecting the EI. The study of Li *et al*. has shown that the 5-year OS rate of Chinese patients with LNM in the supraclavicular region was ~11.0–37.6%[19,23,24]. However, these studies specifically focus on LNM in the supraclavicular region and do not investigate the LNM in stations 104 and 101. The development of minimally invasive esophagectomy (MIE) has allowed for the removal of LNs in station 101 and LNs in station 106 with recurrent perineural invasion, while LNs in station 104 cannot be excised through MIE in two-field lymphadenectomy[25,26]. Hence, further investigation is necessary to determine the necessity of performing three-field LN resection to remove LNs in station 104.

Although the treatment of ESCC is primarily comprehensive, esophagectomy remains the cornerstone of treatment[7,13,20]. However, the role of lymphadenectomy remains controversial in esophagectomy[25–28]. Similar to gastrectomy, the extent of LN dissection continues to expand from D2 to D2 plus and D3 regions, and this expansion remains controversial among researchers[29,30]. The use of two-field and three-field lymphadenectomy techniques in esophagectomy has been a subject of controversy. With the development of MIE, two-field lymphadenectomy has emerged as a safer

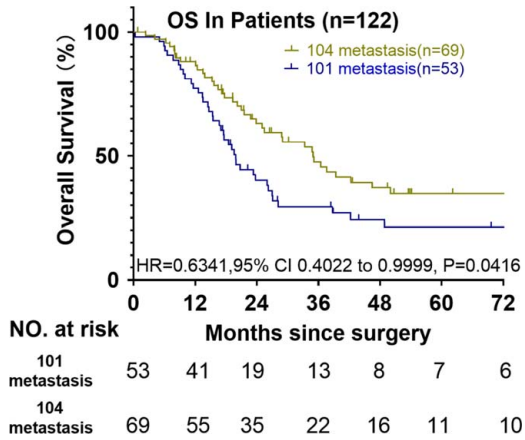

Figure 2. OS analysis of patients with cervical paraesophageal LNM and supraclavicular LNM.

approach for this surgical procedure[25–28]. Many retrospective studies have found that the incidence of complications after three-field LN dissection is high, which limits the development of three-field LN dissection for EC. However, with advancements in anesthesia technology, improvements in surgical techniques, and the implementation of enhanced recovery after surgery protocols, the safety of thoracic ESCC with three-field lymph node dissection has significantly improved. Many medical centers have adopted these practices.[27,31–33].

The current study is limited by including retrospectively collected data solely from a single center. Moreover, the limited number of patients further constrains the generalizability of the findings. To enhance the credibility and verification of our findings, it is essential to foster multi-center collaboration between multiple hospitals in China to obtain larger cohorts.

Conclusions

In conclusion, our retrospective analysis of patients with ESCC who underwent esophagectomy revealed that the location of LNM played a notable role in predicting the OS outcomes. The obtained findings demonstrate that patients with cervical paraesophageal LNM had a significantly worse OS than those with supraclavicular LNM. However, the UICC/AJCC guidelines only put 104 into the M1 stage. Overall, this work provides novel insights into prognostic considerations and treatment decision-making in ESCC.

Ethical approval

All procedures performed in this study were in accordance with the Declaration of

Helsinki (as revised in 2013). The study was approved by the Ethics Committee (EC) for Medical Research and New Medical Technology of Sichuan Cancer Hospital (SCCHEC-02-2022-050). Consent was waived by the Ethics Committee (EC) due to the retrospective nature of the study. Ethical approval for this study (SCCHEC-02-2022-050) was provided by the Medical Research and New Medical Technology of Sichuan Cancer Hospital, Chengdu, China, on 20 April 2022.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

All authors: study concept and design, acquisition, analysis, or interpretation of data; K.L.: drafting of the article and statistical analysis; L.P.: administrative, technical, or material support and obtained funding; Y.H.: study supervision; all authors: revising the article critically for important intellectual content and final approval of the version to be published; K.L., X.L., and W.H.: had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

1. Name of the registry: ClinicalTrials.gov.
2. Unique identifying number or registration ID: NCT06165094.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/ct2/show/NCT06165094?term=NCT06165094&draw=2&rank=1.

Guarantor

Kexun Li and Lin Peng are guarantors.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Due to privacy and ethical considerations, the raw data involving patient information are not publicly available. However, de-identified data can be made available from the corresponding author upon reasonable request and with appropriate ethical approval.

Provenance and peer review

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