Original Article

Patterns of regional lymph node metastasis predict postoperative overall survival and disease-free survival in locally advanced esophageal squamous cell carcinoma

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Background: Lymph nodal characteristics are highly significant in predicting the survival of patients with esophageal squamous cell carcinoma (ESCC). However, there is currently a scarcity of studies examining their role in locally advanced ESCC. In the present study, we attempted to depict the patterns of regional lymph node metastasis and investigate their predictive potential in locally advanced ESCC.

Methods: Patients with locally advanced ESCC underwent esophagectomy at the Department of Thoracic Surgery, The First Affiliated Hospital of Shantou University Medical College were included. Kaplan-Meier curve was used to compare the survival differences between groups. Cox regression was constructed to screen the independent risk factors.

Results: A total of 439 patients were included. We identified 10% as the optimal cutoff value for positive lymph node ratio (PLNR) with X-tile software. Statistically significant differences were found in both overall survival (OS, P<0.001) and disease-free survival (DFS, P<0.001) among different PLNR groups. PLNR [hazard ratio (HR): 1.85, P<0.001] and metastatic lymph nodes along the left gastric artery (HR: 1.63, P=0.02) were the independent prognostic factors for OS. While PLNR (HR: 1.77, P<0.001) and metastatic total main bronchus lymph nodes (HR: 2.78, P=0.047) were the independent prognostic factors for DFS.

Conclusions: We discovered that higher PLNR is associated with poorer OS and DFS of locally advanced ESCC. The lymph nodes along the left gastric artery and the total main bronchus lymph nodes were independent prognosticators for OS and DFS, respectively.

Keywords: Esophageal squamous cell carcinoma (ESCC); prognosis; lymph node metastasis; positive lymph node ratio (PLNR)

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Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related death in the world (1). In China, the predominant type of EC is esophageal squamous cell carcinoma (ESCC) (2). Despite advances in therapeutic strategies, the prognosis of EC remained poor (3). Surgery is the primary mainstream treatment modality for locally advanced ESCC. However, postoperative locoregional recurrences and distant metastasis remains a considerably heavy tumor

burden, which results in dismal overall survival (OS) (4,5) and quality of life (6).

Postoperative positive lymph node number is of great significance in predicting OS of ESCC patients (7). Moreover, the total number of resected lymph nodes (TLNs), representative of the extent of lymphadenectomy, was also shown to be an important prognosticator for surgically resected ESCC (8). The researchers further integrated these two nodal characteristics by calculating the ratio of number of metastatic nodes to the number of resected nodes and named it positive lymph node ratio (PLNR) (9-11). Previous studies have explored the prognostic significance of PLNR in EC (12-14). In addition, the distribution of metastatic lymph nodes may be associated with the various biological features of the primary tumor (15). Differences in the location of metastatic lymph nodes were also reported as a prognostic factor for ESCC (16). However, there is currently limited research dedicated to examining the impact of lymph node-related characteristics on locally advanced ESCC.

The current study set out to investigate the association between the lymph node-related characteristics and prognosis of locally advanced ESCC patients. In addition, we attempted to depict the patterns of regional lymph node metastasis and investigate their predictive ability in assessing postoperative recurrence and distant metastasis.

Highlight box

Key findings

- Positive lymph node ratio (PLNR) is associated with poorer overall survival (OS) and disease-free survival (DFS) in patient with locally advanced esophageal squamous cell carcinoma (ESCC).
- The lymph nodes along the left gastric artery and the total main bronchus lymph nodes were independent prognosticators for OS and DFS in patients with locally advance ESCC, respectively.

What is known and what is new?

- Lymph nodal characteristic is highly significant in predicting the survival of patients with esophageal squamous cell carcinoma.
- In this study, we discovered that the PLNR and specific lymph node metastasis, such as lymph nodes along the left gastric artery and the total main bronchus lymph nodes, hold independent prognostic significance for the survival of patients with locally advanced ESCC.

What is the implication, and what should change now?

- Considering additional lymph node features, such as PLNR and specific lymph node metastasis, can contribute to predicting the prognosis of patients with locally advanced ESCC.

We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-976/rc).

Methods

Study design and patient characteristics

This study was a single-center, retrospective study. A prospectively maintained database of patients with locally advanced ESCC who underwent esophagectomy between January 2010 and November 2019 at the Department of Thoracic Surgery, The First Affiliated Hospital of Shantou University Medical College was reviewed. The patients were enrolled according to the following criteria: (I) pathologically confirmation of ESCC and underwent esophagectomy; (II) ESCC was the primary malignancy; (III) complete and retrievable clinical records. Patients with esophageal adenocarcinoma/adenosquamous carcinoma, M1 disease before surgery, and incomplete medical records which hamper the statistical analyzes were excluded. A flowchart of the study design is shown in *Figure 1*. The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shantou University Medical College (KY-No.2020-094). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As a retrospective study, the need for informed consent was waived by the institutional review board.

Surgery and pathological examination

A radical subtotal esophagectomy with lymphadenectomy was performed in all the enrolled patients. During operation, all dissected lymph nodes stations were identified in individually labeled specimen jars before pathological examination. The surgical specimens were further made into hematoxylin and eosin slides and reviewed by two pathologists independently. The pathologists were blinded to each other's pathological report. The metastatic situation of the following lymph nodes was examined and recorded: cervical lymph nodes, right/left/total recurrent nerve lymph nodes, upper/middle/lower/total thoracic paraesophageal lymph nodes, subcarinal lymph nodes, right/left/total main bronchus lymph nodes, paracardial lymph nodes, lesser/greater curvature lymph nodes, paragastric lymph nodes, lymph nodes along the left gastric artery, lymph nodes along the common hepatic artery, lymph nodes along the abdominal aorta. Criteria for lymph node station

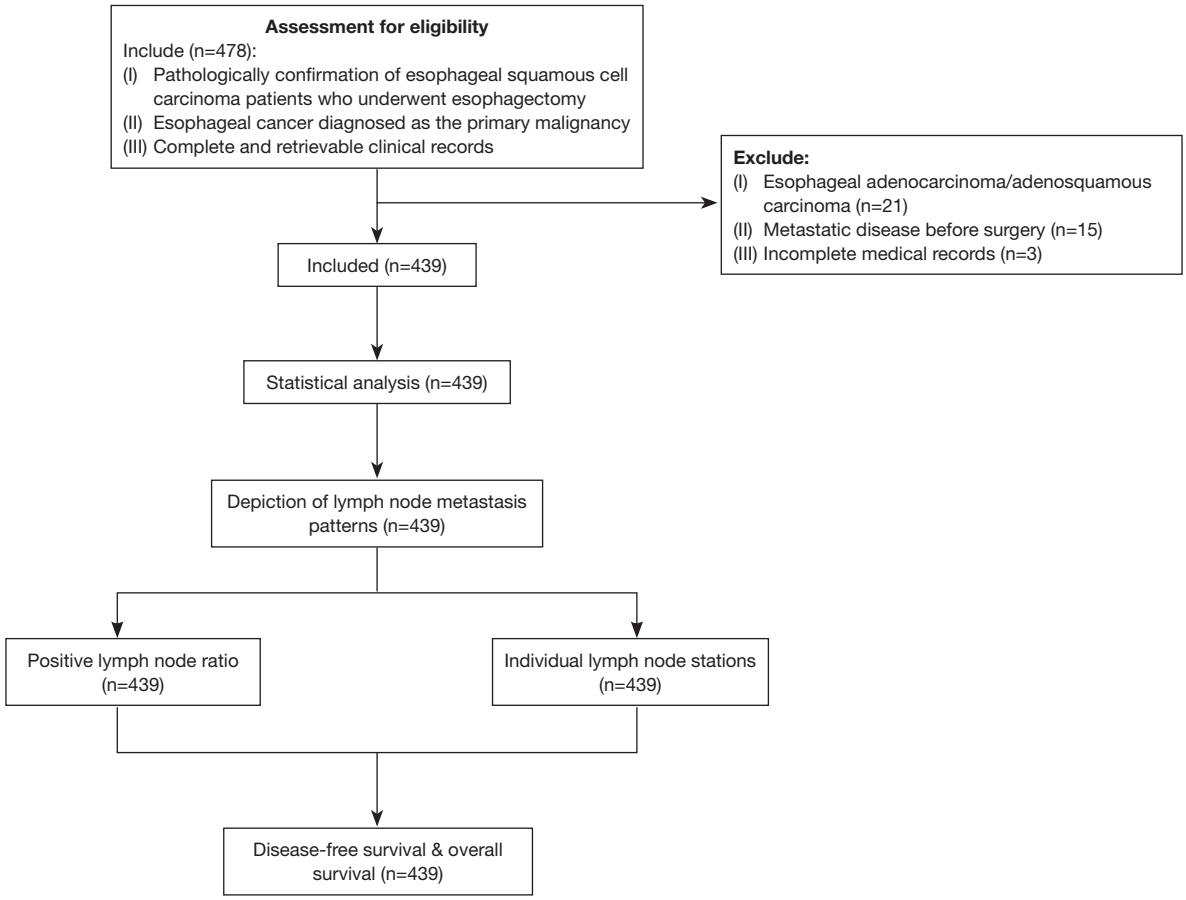

Figure 1 Flowchart of the study design.

classification is based on the 11th edition of the Japanese Classification of Esophageal Cancer (17).

Outcome measures and follow-up information

Clinical endpoints included OS and disease-free survival (DFS). OS was calculated from the date of surgery to the date of death (18). DFS was defined as the time from surgery to the evidence of first recurrence or distant metastasis (18,19). All the participants were followed up postoperatively every 3 months for 1 year, every 6 months for the subsequent 2 years, and annually thereafter. Censored data included living or lost to follow-up individuals at the last follow-up.

Statistical analysis

Comparisons of continuous variables were analyzed using the Student's *t*-test or the Wilcoxon rank sum tests for parametric and non-parametric variables, respectively. Categorical variables were compared by using the Chi-square test or Fisher's exact test. X-tile software was used to determine the optimal cut-off value for continuous variables. Univariate Cox analyzes were performed to identify survival-associated factors, and multivariate Cox regression was constructed to screen the independent risk factors for ESCC. A stepwise forward procedure was adopted in the multivariate regression analyses. Moreover, the Kaplan-Meier method and log-rank test were used to estimate OS/DFS and to compare the survival differences among groups (20). $P<0.05$ (two-sided) was considered statistically significant. All statistical data were analyzed using the software "Statistical Package for Social Science" (SPSS) version 26 for Windows (SPSS Inc., Chicago, IL, USA) and R 4.0.0 (R Core Team 2020). High-quality figures were generated using the R package.

Table 1 Demographic and clinicopathological characteristics of patients (N=439)

Characteristics	Values
Sex	
Male	339 [77]
Female	100 [23]
Age (years)	61 [56–66]
Tumor location	
Thoracic upper portion	50 [11]
Thoracic middle portion	270 [62]
Thoracic lower portion	119 [27]
Grade	
Well differentiation	42 [10]
Moderate differentiation	345 [79]
Poor differentiation	52 [12]
pT	
T1a	9 [2]
T1b	40 [9]
T2	101 [23]
T3	289 [66]
pN	
N0	269 [61]
N1	102 [23]
N2	60 [14]
N3	8 [2]
pTNM	
IB	44 [10]
IIA	113 [26]
IIB	122 [28]
IIIA	20 [5]
IIIB	132 [30]
IVA	8 [2]
Resection	
R0	422 [96]
R1	17 [4]

Values are presented as n [%] or median [interquartile range]. pT, pathological tumor stage; pN, pathological nodal stage; pTNM, pathological TNM stage.

Table 2 Lymph node metastasis status in participants (N=439)

Variables	Values
Cervical lymph nodes	22 (5.01)
Right recurrent nerve lymph nodes	25 (5.69)
Left recurrent nerve lymph nodes	11 (2.51)
Total recurrent nerve lymph nodes	34 (7.74)
Thoracic paraesophageal lymph nodes	53 (12.07)
Subcarinal lymph nodes	44 (10.02)
Total main bronchus lymph nodes	6 (1.37)
Paracardial lymph nodes	40 (9.11)
Lesser curvature lymph nodes	24 (5.47)
Lymph nodes along the left gastric artery	44 (10.02)
Lymph nodes along the abdominal aorta	5 (1.14)

Values are presented as n (%). Only lymph node stations whose metastatic incidences were higher than one percent were presented.

Results

Demographic and clinicopathological characteristics

The clinicopathological characteristics of the study participants are presented in *Table 1*. A total of 439 patients were included. The median age was 61 [interquartile range (IQR), 56–66] years. Over 60% of the primary tumors were located in the middle portion of the thoracic esophagus. In terms of nodal involvement, nearly 40% of the patients had node positive disease, N1 (n=102, 23%), N2 (n=60, 14%) and N3 (n=8, 2%). For recorded metastatic lymph node stations whose incidences were higher than one percent are presented in *Table 2*.

Prognostic significance of PLNR

Using X-tile software, we identified 10% as the optimal cutoff value for PLNR. Patients were divided into Group A, Group B, and Group C according to the level of PLNR: 0%, ≤10%, and >10%, respectively. Significant association between PLNR and tumor location (P=0.02), pathological T stage (P=0.003), pathological N stage (P<0.001) and pathological TNM stage (P<0.001) were found. Kaplan-Meier survival analysis demonstrated significant differences in both OS (P<0.001, *Figure 2A*) and DFS (P<0.001,

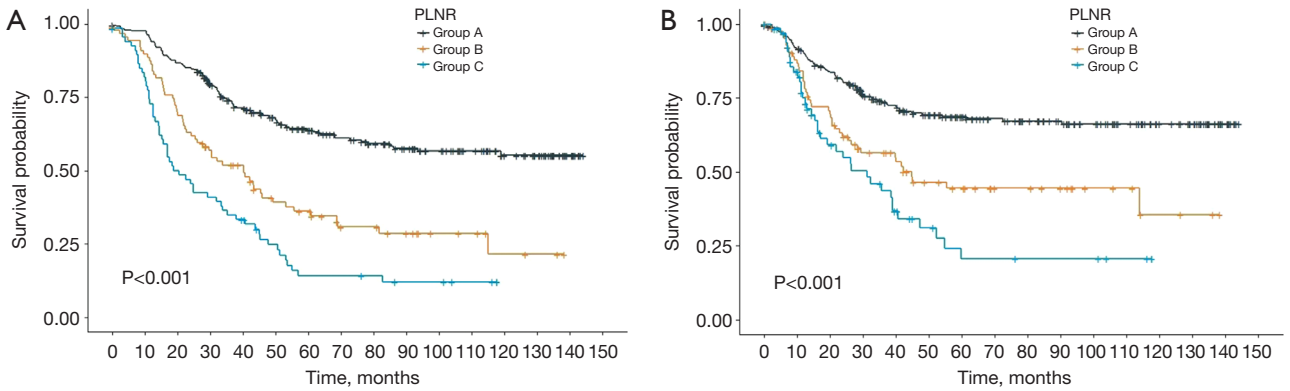

Figure 2 Kaplan-Meier curves for overall survival (A) and disease-free survival (B) among PLNR groups. Patients were divided into Group A, Group B, and Group C according to the level of PLNR: 0%, ≤10%, and >10%, respectively. PLNR, positive lymph node ratio.

Figure 2B) among the three PLNR groups.

Prognostic significance of metastatic lymph node stations

The 11th Japanese Classification of Esophageal Cancer Guideline classified cervico-thoraco-abdominal lymph nodes into 35 stations (17). Considering convenience in statistical analysis and clinical significance, we included lymph node stations whose incidence was higher than one percent in the study population. There is a significant association between PLNR and the following lymph nodes: cervical lymph nodes (P<0.001), right recurrent nerve lymph nodes (P<0.001), left recurrent nerve lymph nodes (P=0.002), total recurrent nerve lymph nodes (P<0.001), thoracic paraesophageal lymph nodes (P<0.001), total main bronchus lymph nodes (P=0.04), subcarinal lymph nodes (P<0.001), paracardial lymph nodes (P<0.001), lesser curvature lymph nodes (P<0.001) and lymph nodes along the left gastric artery (P<0.001). In addition, survival analysis revealed significant differences in OS among cervical lymph nodes [hazard ratio (HR): 1.78, 95% confidence interval (CI): 1.07–2.97, P=0.03], thoracic paraesophageal lymph nodes (HR: 2.41, 95% CI: 1.71–3.40, P<0.001), total main bronchus lymph nodes (HR: 5.16, 95% CI: 2.11–12.61, P<0.001), subcarinal lymph nodes (HR: 2.37, 95% CI: 1.59–3.54, P<0.001), paracardial lymph nodes (HR: 2.49, 95% CI: 1.69–3.65, P<0.001), lesser curvature lymph nodes (HR: 2.52, 95% CI: 1.53–4.15, P<0.001) and lymph nodes along the left gastric artery (HR: 2.81, 95% CI: 1.93–4.09, P<0.001) (*Table 3*).

In terms of DFS, significant survival differences among total recurrent lymph nodes (HR: 2.24, 95% CI: 1.36–3.68, P=0.001), thoracic paraesophageal lymph nodes (HR: 2.28, 95% CI: 1.53–3.41, P<0.001), total main bronchus lymph nodes (HR: 2.31, 95% CI: 1.71–12.60, P=0.003), subcarinal lymph nodes (HR: 4.64, 95% CI: 1.18–3.10, P=0.008), paracardial lymph nodes (HR: 1.91, 95% CI: 1.46–3.67, P<0.001), lesser curvature lymph nodes (HR: 2.43, 95% CI: 1.35–4.39, P=0.003) and lymph nodes along the left gastric artery (HR: 2.51, 95% CI: 1.64–3.85, P<0.001) were observed (*Table 3*).

Independent prognostic factors for ESCC

Through univariate analysis, PLNR (HR: 1.99, 95% CI: 1.69–2.34, P<0.001) and the above mentioned lymph node stations were identified as key prognostic factors for OS. Among these prognosticators, PLNR (HR: 1.85, 95% CI: 1.55–2.21, P<0.001) and metastatic lymph nodes along the left gastric artery (HR: 1.63, 95% CI: 1.10–2.42, P=0.02) were identified as the independent prognostic factors (*Table 3*). For DFS, univariate and multivariate analyses showed that PLNR (HR: 1.77, 95% CI: 1.46–2.14, P<0.001) and metastatic total main bronchus lymph nodes (HR: 2.78, 95% CI: 1.01–7.65, P=0.047) were the independent prognostic factors (*Table 3*). To compare the diagnostic effects of the above model and the American Joint Committee of Cancer (AJCC) 8th edition pathologic N in ESCC, we plotted 1-year ROC curves of the two models and compared their area under curve (AUC) values. ROC curve results indicated that the long-term AUC level of PLNR and metastatic lymph nodes along the left gastric artery (AUC =0.705) was higher than golden

Table 3 Univariate and multivariate cox regression analysis of OS and DFS of ESCC patients

Variables	OS				DFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Sex	0.95 (0.69–1.32)	0.77	–	–	0.85 (0.58–1.26)	0.42	–	–
Tumor location	1.12 (0.89–1.42)	0.34	–	–	1.16 (0.89–1.51)	0.28	–	–
Grade	1.42 (1.08–1.89)	0.01	–	–	1.30 (0.94–1.81)	0.11	–	–
pT	1.24 (1.02–1.50)	0.04	–	–	1.16 (0.94–1.45)	0.17	–	–
pN	1.85 (1.59–2.15)	<0.001	–	–	1.66 (1.40–1.98)	<0.001	–	–
pTNM	1.47 (1.33–1.62)	<0.001	–	–	1.37 (1.22–1.53)	<0.001	–	–
PLNR	1.99 (1.69–2.34)	<0.001	1.85 (1.55–2.21)	<0.001	1.80 (1.49–2.18)	<0.001	1.77 (1.46–2.14)	<0.001
Cervical LN	1.78 (1.07–2.97)	0.03	–	–	1.71 (0.95–3.09)	0.07	–	–
Right recurrent nerve LN	1.34 (0.73–2.48)	0.34	–	–	1.79 (0.99–3.23)	0.06	–	–
Left recurrent nerve LN	1.68 (0.75–3.81)	0.21	–	–	2.20 (0.97–4.98)	0.06	–	–
Total recurrent nerve LN	1.64 (0.99–2.71)	0.06	–	–	2.24 (1.36–3.68)	0.001	–	–
Thoracic paraesophageal LN	2.41 (1.71–3.40)	<0.001	–	–	2.28 (1.53–3.41)	<0.001	–	–
Subcarinal LN	2.37 (1.59–3.54)	<0.001	–	–	4.64 (1.18–3.10)	0.008	–	–
Total main bronchus LN	5.16 (2.11–12.61)	<0.001	–	–	2.31 (1.71–12.60)	0.003	2.78 (1.01–7.65)	0.047
Paracardial LN	2.49 (1.69–3.65)	<0.001	–	–	1.91 (1.46–3.67)	<0.001	–	–
Lesser curvature LN	2.52 (1.53–4.15)	<0.001	–	–	2.43 (1.35–4.39)	0.003	–	–
LN along the left gastric artery	2.81 (1.93–4.09)	<0.001	1.63 (1.10–2.42)	0.02	2.51 (1.64–3.85)	<0.001	–	–
LN along the abdominal aorta	1.30 (0.42–4.07)	0.650	–	–	1.68 (0.54–5.27)	0.37	–	–

OS, overall survival; DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; pT, pathological tumor stage; pN, pathological nodal stage; pTNM, pathological TNM stage; PLNR, positive lymph node ratio; LN, lymph node; HR, hazard ratio; CI, confidence interval.

standard (AUC =0.674) (Figure S1).

Discussion

Nodal characteristics such as positive lymph node stations, positive lymph node number, TLNs and PLNR has been reported to associate with prognosis of patients diagnosed with locally advanced ESCC (10,11,15,16). Postoperative local recurrence and distant metastasis are still heavy postoperative burdens which also affect both patients quality of life (6) and life span (4,5). Currently, few studies have addressed the specific relationship between nodal characteristics and these postoperative events. We conducted a retrospective cohort study, aiming at investigating the association between lymph node-related characteristics and postoperative survival of ESCC patients.

In this study, we discovered that PLNR is a significant prognostic factors for OS and DFS. The optimal cut-off value was 10%. Yao *et al.* reported that PLNR ≥0.16 is an independent prognostic factor for OS in ESCC patients according to the data in public database (21). Similarly, Melis *et al.* also reported that PLNR is a negative predictor for OS (22). Furthermore, Shao *et al.* proposed that PLNR could supplement the pN categorization system for better prognostic assessment (9). Together with these results, our findings indicated that PLNR plays an essential role in predicting both long-term OS as well as undesired postoperative events such as local recurrence and distant metastasis. However, different cutoff values were selected in these studies. This may be due to difference in the enrolled participants and varied sample sizes. Further large-scale studies are needed to address this issue.

Our study also discovered that a number of lymph node stations whose metastatic status was significantly associated with prognosis. Among the investigated lymph node stations, the lymph nodes along the left gastric artery and the total main bronchus lymph nodes were revealed to be independent prognosticators for OS and DFS, respectively. Deng *et al.* concluded that dissection of the left gastric lymph nodes is essential based on the carbon nanoparticle labeling of the lymphatic drainage pathway of esophageal carcinomas (16). Liu *et al.* also reported that lymph node metastasis along the left gastric artery in ESCC is an important independent prognostic factor for cancer-specific survival (23). In contrast to these studies, we pointed out that left gastric lymph node metastasis only predicts OS but not cancer-specific local recurrence and distant metastasis, and that total main bronchus lymph node metastasis is more likely to be significantly associated with DFS.

Although the findings should be interpreted with caution, this study has several advantages. First, it included a fairly large sample size with complete long-term follow-up information. Second, based on the previous findings, this study further explains the interaction between PLNR and the individual metastatic lymph node stations.

However, this study also has several limitations. First, the retrospective nature of this study could introduce potential selection biases. Second, the lack of external validation cohort may affect the robustness of the prognostic models for OS and DFS.

Conclusions

In conclusion, we discovered that higher PLNR, particularly at a cutoff value of 10%, is associated with poorer OS and DFS. In addition, the lymph nodes along the left gastric artery and the total main bronchus lymph nodes were revealed to be independent prognosticators for OS and DFS, respectively. Future multicenter, prospective research is required to validate these findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-976/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-976/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-976/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shantou University Medical College (KY-No.2020-094). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As a retrospective study, the need for informed consent was waived by the institutional review board.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. He F, Wang J, Liu L, et al. Esophageal cancer: trends in incidence and mortality in China from 2005 to 2015. Cancer Med 2021;10:1839-47.
3. Lee TS, Song IH, Shin JI, et al. PET Imaging Biomarkers of Anti-EGFR Immunotherapy in Esophageal Squamous Cell Carcinoma Models. Cells 2018;7:187.
4. Ohashi S, Miyamoto S, Kikuchi O, et al. Recent Advances

From Basic and Clinical Studies of Esophageal Squamous Cell Carcinoma. Gastroenterology 2015;149:1700-15.
5. Schreiber D, Rineer J, Vongtama D, et al. Impact of postoperative radiation after esophagectomy for esophageal cancer. J Thorac Oncol 2010;5:244-50.
6. Chang YL, Tsai YF, Chao YK, et al. Quality-of-life measures as predictors of post-esophagectomy survival of patients with esophageal cancer. Qual Life Res 2016;25:465-75.
7. Hagens ERC, van Berge Henegouwen MI, Cuesta MA, et al. The extent of lymphadenectomy in esophageal resection for cancer should be standardized. J Thorac Dis 2017;9:S713-23.
8. Altorki NK, Zhou XK, Stiles B, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg 2008;248:221-6.
9. Shao Y, Geng Y, Gu W, et al. Assessment of Lymph Node Ratio to Replace the pN Categories System of Classification of the TNM System in Esophageal Squamous Cell Carcinoma. J Thorac Oncol 2016;11:1774-84.
10. Zhang H, Liang H, Gao Y, et al. Metastatic lymph node ratio demonstrates better prognostic stratification than pN staging in patients with esophageal squamous cell carcinoma after esophagectomy. Sci Rep 2016;6:38804.
11. Smit JK, Pultrum BB, van Dullemen HM, et al. Prognostic factors and patterns of recurrence in esophageal cancer assert arguments for extended two-field transthoracic esophagectomy. Am J Surg 2010;200:446-53.
12. Raman V, Jawitz OK, Farrow NE, et al. The Relationship Between Lymph Node Ratio and Survival Benefit With Adjuvant Chemotherapy in Node-positive Esophageal Adenocarcinoma. Ann Surg 2022;275:e562-7.
13. Li Y, Zhao W, Ni J, et al. Predicting the Value of Adjuvant Therapy in Esophageal Squamous Cell Carcinoma by Combining the Total Number of Examined Lymph Nodes with the Positive Lymph Node Ratio. Ann Surg Oncol 2019;26:2367-74.
14. Liu YP, Ma L, Wang SJ, et al. Prognostic value of lymph node metastases and lymph node ratio in esophageal squamous cell carcinoma. Eur J Surg Oncol 2010;36:155-9.
15. Hagens ERC, van Berge Henegouwen MI, van Sandick JW, et al. Distribution of lymph node metastases in esophageal carcinoma [TIGER study]: study protocol of a multinational observational study. BMC Cancer 2019;19:662.
16. Deng XM, Zhu TY, Wang GJ, et al. Lymph node metastasis pattern and significance of left gastric artery lymph node dissection in esophagectomy for esophageal cancers. World J Surg Oncol 2021;19:296.
17. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus 2017;14:1-36.
18. Terashima Y, Toda E, Itakura M, et al. Targeting FROUNT with disulfiram suppresses macrophage accumulation and its tumor-promoting properties. Nat Commun 2020;11:609.
19. Zhao SG, Chang SL, Erho N, et al. Associations of Luminal and Basal Subtyping of Prostate Cancer With Prognosis and Response to Androgen Deprivation Therapy. JAMA Oncol 2017;3:1663-72.
20. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252-9.
21. Yao W, Lu N, Cui M, et al. Positive lymph node ratio ≥0.16 is an independent risk factor affecting the prognosis of patients with esophageal cancer. Nan Fang Yi Ke Da Xue Xue Bao 2020;40:837-42.
22. Melis M, Masi A, Pinna A, et al. Does lymph node ratio affect prognosis in gastroesophageal cancer? Am J Surg 2015;210:443-50.
23. Liu X, Wu L, Zhang D, et al. Prognostic impact of lymph node metastasis along the left gastric artery in esophageal squamous cell carcinoma. J Cardiothorac Surg 2021;16:124.

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