

# Prognostic significance of middle paraesophageal lymph node metastasis in resectable esophageal squamous cell carcinoma

## A STROBE-compliant retrospective study

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### Abstract

Lymph node metastasis (LNM) of esophageal squamous cell carcinoma (ESCC) has important prognostic significance. In this study, we examined the correlations between lymph node metastatic sites and prognosis in patients with resectable ESCC.

A total of 960 patients who received curative esophagectomy with systemic lymphadenectomy between 1996 and 2014 were included in the retrospective analysis. The Kaplan-Meier method and log-rank test were used to perform the survival analysis. The prognostic significance of LNM site was evaluated by Cox regression analysis.

The LNM in middle paraesophageal ( $P < .001$ ), subcarinal ( $P < .001$ ), lower paraesophageal ( $P < .001$ ), recurrent laryngeal nerve ( $P = .012$ ), paratracheal ( $P = .014$ ), and perigastric ( $P < .001$ ) sites were associated with poor prognosis in univariate analysis. In multivariate analysis, only middle paraesophageal LNM (MPLNM,  $P = .017$ ; HR, 1.33; 95%CI, 1.05–1.67) was the independent factor for worse prognosis. Additionally, patients with MPLNM had a lower 5-year survival rate (15.6%) than those with LNM at other sites. Furthermore, upper or middle tumor location and relatively late pN stage were associated with increased risk of MPLNM.

Our findings suggested MPLNM could be a characteristic indicating the worst prognosis. Preoperative examinations should identify the existences of MPLNM, especially on patients with risk factors. And patients with MPLNM should be considered for more aggressive multidisciplinary therapies.

**Abbreviations:** AJCC = American Joint Committee Cancer, ESCC = esophageal squamous cell carcinoma, JCEC = Japanese Classification of Esophageal Cancer, LNM = lymph node metastasis, MPLNM = middle paraesophageal lymph node metastasis, OS = overall survival, PET-CT = positron emission tomography-computed tomography.

**Keywords:** esophageal squamous cell carcinoma, paraesophageal lymph node, prognosis

## 1. Introduction

Esophageal cancer is the eighth most common cancer in the world, with more than 456,000 new cases and 400,000 deaths occurring annually.<sup>[1]</sup> Esophageal squamous cell carcinoma (ESCC), accounting for almost 80% of esophageal cancer, is

the major histological subtype worldwide.<sup>[2]</sup> Lymph node metastasis (LNM) is the most important prognostic factor for patients with ESCC.<sup>[3,4]</sup> According to The 7th edition of the American Joint Committee Cancer (AJCC) Staging System, pathological N staging is depended on the exact number of positive lymph nodes after surgery. However, the overall survival (OS) can be discrepant among patients with same numbers of LNM. One possible explanation for the difference is that LNM sites that are not considered in pN staging are another significant impact factor for prognosis. Thus, further clarifications of the clinical significance of LNM site may contribute to individual, and more accurate tumor staging, which would be important basis for patient diagnosis and treatment.

There has been controversy on impacts of LNM sites on the prognosis of ESCC patients. Wu et al<sup>[5]</sup> suggested that the sites of metastatic lymph nodes were not independent prognostic risk factors in ESCC. While the involvements of subcarinal and lower paraesophageal lymph nodes were independent prognostic factors in ESCC recurrence<sup>[6]</sup> and long-term survival.<sup>[7]</sup> Compared with AJCC staging system, the 10th edition of the Japanese Classification of Esophageal Cancer (JCEC) categorizes N stage considering both the site and the number of the metastatic lymph nodes.

In addition, the risk factors associated with LNM in certain site are largely unclear. If the potential prognostic impacts of LNM sites could be found, then a better understanding of risk factors for different sites of LNM would also be the key to identify a

Editor: Monica Casiraghi.

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The authors declare that they have no conflicts of interest.

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How to cite this article: Hong H, Jie H, Liyu R, Zerui C, Borong S, Hongwei L. Prognostic significance of middle paraesophageal lymph node metastasis in resectable esophageal squamous cell carcinoma. *Medicine* 2019;98:43(e17531).

Received: 15 May 2019 / Received in final form: 23 August 2019 / Accepted: 9 September 2019

<http://dx.doi.org/10.1097/MD.00000000000017531>

subgroup of patients with prognostic relevance. Since the tumors are too complex, the survival outcomes are difficult to be predicted. Therefore, a number of studies have been devoted to explore new ways to understand tumor prognosis. The LNM in middle paraesophageal region is a common phenomenon in ESCC but has not been fully studied. In this study, we analyzed the clinical data of 960 consecutive patients with thoracic ESCC to investigate the prognostic significance of MPLNM in ESCC.

## 2. Materials and methods

### 2.1. Patient selection

The 960 patients with histological diagnosed ESCC receiving surgery at the Department of Thoracic Surgery of Guangdong General Hospital, Guangzhou, China between December 1996 and December 2014 were included in the retrospective cohort for analysis. All of the patients involved must meet the following criteria: primary tumor and histologically identified squamous cell carcinoma of the thoracic esophagus; R0 esophagectomy without preoperative chemo- or radio-therapy; patients had positive LNM; the records contained sufficient information for analysis.

The exclusion criteria were:

1. esophageal adenocarcinoma, small cell carcinoma, or leiomyosarcoma;
2. the patient had history of other malignant diseases;
3. fewer than 7 lymph nodes examined in the surgery (according to AJCC pN staging system); patients died of postoperative complications within 30 days.

All lymph nodes were dissected separately during surgery and analyzed by pathologists. The AJCC staging manual (7th edition) was used in this analysis. The study was approved by the medical ethics committee of South China University of Technology research institutes, Guangzhou, China.

### 2.2. Preoperative workup, surgical procedure, and follow-up

Preoperative patient evaluations include history taking, physical examination, endoscopy of the entire upper gastrointestinal tract, chest CT and ultrasonography/CT of neck and abdomen and pathological diagnosis. Other preoperative evaluations included endoscopic ultrasonography, and esophagography.

The patients with stage cTis–T4aN0–2 tumors without distal metastases received surgery. The location of primary tumor was classified as the upper, middle, or lower esophageal tract according to the 7th edition of AJCC cancer staging system. The pathologic TNM stage of esophageal cancer was determined using the same system.

R0 esophagectomy with lymph node dissection was performed on patients with resectable ESCC. Cervical lymph node sampling was routinely performed during the surgery when patients received the left transthoracic or the tri-incisional procedure. The dissected cervical lymph nodes included supraclavicular, cervical paraesophageal, and deep cervical nodes. The thoracic LNs included the paraesophageal recurrent nerve, hilar, subcarinal, pulmonary ligament, diaphragmatic, and paratracheal nodes were dissected. The abdominal lymph nodes that were dissected included the paragastric, celiac trunk, splenic artery and hepatic artery nodes.

The patients were followed every month for the first 3 months, then every 3 months for the first year and subsequently every 6 months for the next 2 years and finally annually. The diagnostic examinations consisted of esophagography, CT, chest X-ray,

blood tumor biomarker test, and bone scan or cranial MRI scan when necessary to detect recurrence and/or metastasis. The follow-up was last until death or up to 5 years after surgery for all patients in the study cohort.

### 2.3. Statistical analysis

The statistical analyses were performed using the SPSS 19.0 software package (SPSS Standard version 19.0, SPSS, Chicago, IL). The length of OS was calculated as the time from date of surgery to date of death or final clinical follow-up. The distribution differences of baseline characteristics were compared with Pearson  $\chi^2$  test. The Kaplan-Meier method and log-rank test was used to perform the survival analysis. The prognostic significance of LNM sites was evaluated by univariate Cox regression and parameters that were found to be significant were further assessed by multivariate Cox regression analysis. A  $P < .05$  was considered to be statistically significant.

## 3. Results

### 3.1. Patient characteristics

A total of 960 patients were included in the analysis according to the inclusion and exclusion criteria. The mean age of the patient cohort was 58.1 years (range, 30–88 years), and 777 patients were male gender (80.9%). The distribution of pT stages were pTis, 1 28 (2.9%), pT2 183 (19.1%), pT3 722 (75.2%), and pT4a 27 (2.8%). Among all these cases, 519 (54.1%) cases were in pN1 stage, 322 (33.5%) were in pN2 stage, and 119 (12.4%) were in pN3 stage. A mean of  $16.83 \pm 9.48$  (range, 7–86) lymph nodes per patient were dissected during pathological review, with mean  $3.59 \pm 4.11$  (range, 1–40) positive metastatic lymph nodes per case. The clinicopathological characteristics of the entire cohort were summarized in Table 1.

**Table 1**  
Clinicopathological characteristics of 960 patients included in the retrospective cohort.

Variables	No. of patients <sup>1</sup> (%)
Age <sup>2</sup>	
<58/≥58	446 (46.5)/ 514 (53.5)
Gender	
Male/ Female	777 (80.9)/ 183 (19.1)
Differentiation	
Grade 1/Grade 2/Grade 3	171 (17.8)/ 408 (42.5)/ 381 (39.7)
Tumor location	
upper/middle/lower	151 (15.7)/ 441 (45.9)/ 368 (38.3)
pT stage	
Tis, 1/T2/T3/T4a	28 (2.9)/ 183 (19.1)/ 722 (75.2)/ 27 (2.8)
pN stage	
N1/N2/N3	519 (54.1)/ 322 (33.5)/ 119 (12.4)
Site of LNM <sup>3</sup> (Yes/ No)	
Recurrent laryngeal nerve	100 (10.4)/ 860 (89.6)
Paratracheal	80 (8.3)/ 880 (91.7)
Upper paraesophageal	62 (6.5)/ 898 (93.5)
Middle paraesophageal	232 (24.2)/ 728 (75.8)
Lower paraesophageal	168 (17.5)/ 792 (82.5)
Subcarinal	196 (20.4)/ 764 (79.6)
Perigastric	362 (37.7)/ 598 (62.3)
Celiac	20 (2.1)/ 940 (97.9)

<sup>1</sup> Number of patients; <sup>2</sup>The age of 58 was the mean age and therefore selected as a cut-off value; <sup>3</sup> LNM = Lymph Node Metastasis.

**Table 2**  
**Univariate analysis for overall survival of patients with resectable esophageal squamous cell carcinoma.**

Variables	Univariate analysis			5-year overall survival	
	HR <sup>1</sup>	95% CI <sup>2</sup>	P value	Survival, %	Median, mo <sup>3</sup>
Age (< 58 vs ≥58) <sup>4</sup>	0.91	0.79–1.05	0.207	46.3 vs 43.0	45.8 vs 40.8
Gender (Male vs Female)	1.15	0.97–1.37	0.105	43.9 vs 47.4	42.3 vs 51.3
pT Stage					
Tis, 1	1.00	<sup>5</sup>	–	75.8	NR <sup>6</sup>
T2	2.49	1.67–3.70	<0.001	50.7	NR
T3	3.58	2.45–5.24	<0.001	37.6	33.8
T4a	5.00	2.76–9.04	<0.001	31.3	21.7
pN Stage					
N1	1.00	–	–	56.4	NR
N2	2.11	1.78–2.49	<0.001	29.1	27.3
N3	3.21	2.64–3.91	<0.001	17.1	19.7
Differentiation					
Grade 1, 2	1.00	–	–	48.5	54.8
Grade 2	1.49	1.28–1.75	<0.001	33.7	30.0
Tumor location					
Upper	1.00	–	–	44.9	45.4
Middle	1.03	0.83–1.29	0.771	44.4	43.4
Lower	1.01	0.84–1.23	0.873	44.7	39.9
Site of LNM <sup>7</sup>					
Recurrent laryngeal nerve	1.68	1.12–2.53	<b>0.012</b>	20.4	27.2
Paratracheal	1.87	1.34–3.06	<b>0.014</b>	16.3	23.7
Upper paraesophageal	1.20	0.73–1.97	0.466	42.8	23.6
Middle paraesophageal	2.31	1.87–2.85	<0.001	<b>15.6</b>	<b>19.0</b>
Lower paraesophageal	1.80	1.36–2.38	<0.001	27.2	23.4
Subcarinal	2.13	1.66–2.73	<0.001	20.4	19.7
Perigastric	1.93	1.59–2.34	<0.001	23.4	22.9
Celiac	1.31	0.77–2.22	0.323	16.8	40.7

<sup>1</sup>HR, Hazard Ratio; <sup>2</sup>95%CI, 95% Confidence Interval; <sup>3</sup>mo, Months; <sup>4</sup>The age of 58 was the mean age and therefore selected as a cut-off value; <sup>5</sup>–, data not shown; <sup>6</sup>NR, no reached; <sup>7</sup>LNM = Lymph Node Metastasis.

### 3.2. Prognostic significance of LNM sites

In order to investigate whether the sites of LNM could be prognostic factors in resectable ESCC, we first performed Cox univariate analyses. The results demonstrated that middle paraesophageal ( $P < .001$ ), lower paraesophageal ( $P < .001$ ), recurrent laryngeal nerve ( $P = .012$ ), perigastric ( $P < .001$ ), subcarinal ( $P < .001$ ), and paratracheal ( $P = .014$ ) LNM were correlated with significantly poorer 5-year OS. Among other clinicopathological characteristics, including pT stages ( $P < .001$ ), pN stages ( $P < .001$ ), and tumor differentiations ( $P < .001$ ) were also associated with the worse 5-year OS (Table 2).

Multivariate analysis was performed with Cox proportional hazards model. The results showed that MPLNM ( $P = .017$ ; HR, 1.33; 95%CI, 1.05–1.67) was significantly associated with the poor OS. pT ( $P < .001$ ) and pN ( $P < .001$ ) stages were also independent prognostic factors (Table 3).

The median follow-up was 20.4 months, ranging from 1.07 to 60.0 months. Patients with MPLNM had a 5-year cumulative survival rate of 15.6%, which was significantly lower than the 46.7% survival rate in those without MPLNM ( $P < .001$ , Fig. 1A). Furthermore, the survival difference still existed when stratified by pN stage (Fig. 1B, C). Interestingly, the 5-year survival of patients with MPLNM was also lower than those with LNM in other regions (Table 2).

### 3.3. Risk factors for MPLNM in ESCC

Among 960 patients with LNM, a number of 232 (24.2%) were observed to have MPLNM. The patients with upper or middle

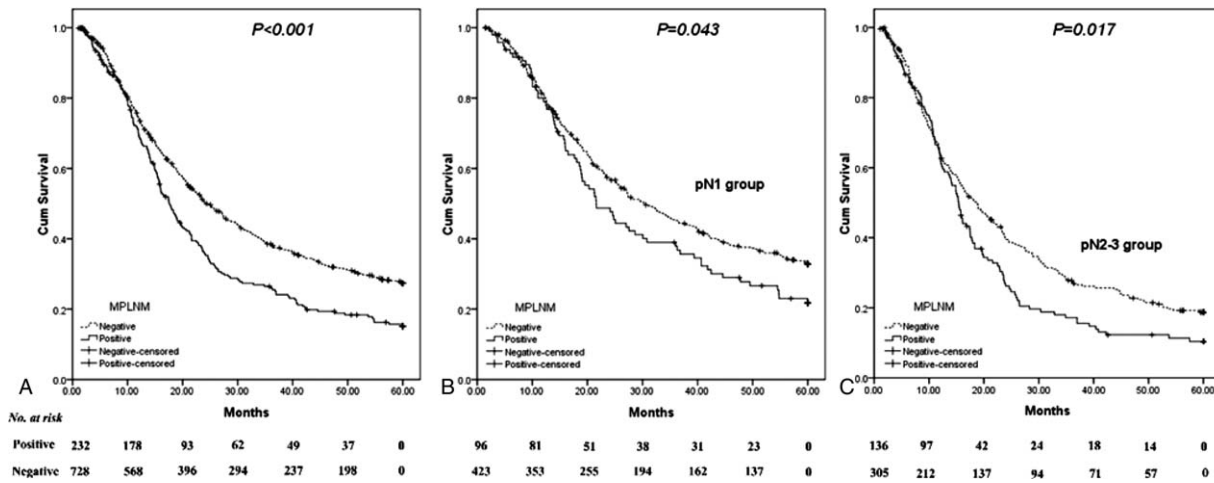
tumor location ( $P < .001$ ), higher pT ( $P < .001$ ) and pN ( $P < .001$ ) stages were associated with MPLNM (Table 4).

The significant variables in Table 4 were included in a logistic regression analysis. The results showed that upper (upper vs lower, OR=3.08;  $P < .001$ ) or middle (middle vs lower, OR=3.75;  $P < .001$ ) tumor location, and relatively late pN stages (pN1 vs pN3, OR=0.244,  $P < .001$ ; pN2 vs pN3, OR=0.462,  $P = .002$ ) were associated with increased risk of MPLNM in ESCC.

**Table 3**  
**The middle paraesophageal lymph node metastasis is an independent prognostic factor in resectable esophageal squamous cell carcinoma.**

Variables	HR <sup>1</sup>	95%CI <sup>2</sup>	P value
pT stage			
pTis <sup>1</sup>	1.00	<sup>3</sup>	–
pT2	2.20	1.48–3.28	<0.001
pT3	2.84	1.94–4.18	<0.001
pT4	4.62	2.55–8.38	<0.001
pN stage			
pN1	1.00	–	–
pN2	1.79	1.50–2.14	<0.001
pN3	2.57	2.07–3.18	<0.001
MPLNM <sup>4</sup>			
Negative	1.00	–	–
Positive	1.33	1.05–1.67	<b>0.017</b>

<sup>1</sup>HR, Hazard Ratio; <sup>2</sup>95%CI, 95% Confidence Interval; <sup>3</sup>–, data not shown; <sup>4</sup>MPLNM, middle paraesophageal lymph node metastasis.



**Figure 1.** The overall survival curves of patients with or without MPLNM. Patients with MPLNM had a significantly lower cumulative 5-year overall survival (A, 15.6% vs 46.7%;  $P < .001$ ); the subgroup analysis by pN stage revealed that MPLNM was still correlated with the worse OS among patients at pN1 (B) or pN2-3 (C) stage, respectively.

#### 4. Discussion

Nowadays, the AJCC staging system is the foundation of ESCC treatment for oncologists. However, since the common pathologic type of esophageal cancer in Asia is squamous cell carcinoma and Asia patients constitute only 25.2% of the cohort that used to elaborate the AJCC system,<sup>[8]</sup> more patient data from Asia on the ESCC staging, prognosis, and therapeutic selection should be valuable to test and improve AJCC system for ESCC.

**Table 4**  
The clinicopathological characteristics of patients with or without middle paraesophageal lymph node metastasis.

Variables	MPLNM1 (%)		P value
	Positive (n = 232)	Negative (n = 728)	
Age <sup>2</sup>			
≥58	126 (24.5)	388 (75.5)	0.787
<58	106 (23.8)	340 (76.2)	
Gender			
Male	183 (25.6)	594 (74.4)	0.359
Female	49 (26.8)	134 (73.2)	
Tumor location			
upper	46 (30.5)	105 (69.5)	<0.001
middle	156 (35.4)	285 (64.6)	
lower	30 (8.2)	338 (91.8)	
Differentiation			
Well	47 (27.5)	124 (72.5)	0.307
Moderate	102 (25.0)	306 (75.0)	
Poor	83 (21.8)	298 (78.2)	
pT stage			
Tis <sup>1</sup>	7 (25.0)	21 (75.0)	<0.001
T2	40 (21.9)	143 (78.1)	
T3	167 (23.1)	555 (76.9)	
T4a	18 (66.7)	9 (33.3)	
pN stage			
pN1	96 (18.5)	423 (81.5)	<0.001
pN2	94 (29.2)	228 (70.8)	
pN3	42 (35.3)	77 (64.7)	

<sup>1</sup> MPLNM, middle paraesophageal lymph node metastasis; <sup>2</sup> The age of 58 was the mean age and therefore selected as a cut-off value.

LNM is the most important prognostic factor for patients with ESCC.<sup>[9,10]</sup> However, there is a contradictory on the prognostic significance of LNM locations between the AJCC and JCEC staging system. Comparing with the sites, the exact number of metastatic lymph nodes was much more difficult to be identified in clinical practice. Currently, positron emission tomography-computed tomography (PET-CT) is a more reliable modality for accurate N staging (with an accuracy range of 61.6%–78.6%).<sup>[11,12]</sup> Yet, the number of LNM in PET/CT may not be accurate as well, and the false negative prediction rate is about 30%.<sup>[13–15]</sup> Especially for lymph nodes smaller than 1 cm in diameter, PET/CT cannot determine the characteristics.<sup>[11,15]</sup> Moreover, the number of metastatic lymph nodes cannot be precisely calculated when the multinodular fusion occurred. Therefore, it is of great clinical significance if the association between the site of LNM and prognosis can be identified.

In the study, we concluded that the MPLNM was an independent prognostic factor for resectable ESCC patients. Although the underlying mechanisms for the poor OS in MPLNM patients are unknown, several studies have found similar associations between LNM sites and prognosis. In clear cell renal cell carcinoma, the interaortocaval LNM represented an independent predictor of cancer specific mortality.<sup>[16]</sup> And in gastric cancer, the central lymph node metastasis was identified to be an adverse prognostic factor.<sup>[17]</sup> Different cancer types may have various biological characteristics, which determine the impacts of LNM sites.

However, several previous researches have discussed the association between LNM sites and prognosis of ESCC patients. Our study is consistent with data from Liu et al,<sup>[18]</sup> who reported that subcarinal metastasis was correlated with poorer OS ( $P < .001$ ), but the independent prognostic significance of subcarinal metastasis was not found. In addition, LNM near the celiac trunk was found to be associated with adverse prognosis in ESCC.<sup>[19]</sup> Therefore, the locations of LNM may have potential prognostic effects in ESCC.

To our best knowledge, no previous research had reported the prognostic role of MPLNM in ESCC. It is notable that the 5-year cumulative survival of patients with MPLNM was much worse than those with LNM in other sites. Therefore, the clinical

significance of MPLNM may not be equivalent to other sites of LNM. As preoperative chemoradiotherapy has recently been shown to extend the length of OS in resectable ESCC,<sup>[20–22]</sup> further studies should investigate whether the prognosis of patients with MPLNM would be improved by taking the preoperative chemoradiotherapy.

The study has several limitations. First, as a retrospective study, there may be some bias in between-group comparison of survival, although our study cohort is relatively large; in addition, the study relies exclusively on data from a single institution. Therefore, future multi-center studies is necessary to test the results.

## 5. Conclusion

In conclusion, MPLNM is an independent prognostic factor for patients with resectable ESCC and receiving surgery. Patients with MPLNM had a poor prognosis, and the 5-year OS was lower than those with LNM in other sites. Thus, to improve the prognosis of patients with MPLNM, more aggressive preoperative multidisciplinary therapies should be considered.

## Author contributions

**Conceptualization:** Hou Jie, Chen Zerui, Shu Borong, Liang Hongwei.

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**Writing – review & editing:** Shu Borong, Liang Hongwei.

## References

- [1] Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
- [2] Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; 349:2241–52.
- [3] Kayani B, Zacharakis E, Ahmed K, et al. Lymph node metastases and prognosis in oesophageal carcinoma—a systematic review. *Eur J Surg* 2011;37:747–53.
- [4] Kunisaki C, Makino H, Kimura J, et al. Impact of lymph-node metastasis site in patients with thoracic esophageal cancer. *J Surg Oncol* 2010; 101:36–42.
- [5] Wu N, Chen Z, Pang L, et al. Prognostic significance of lymph node characteristics on survival in esophageal squamous cell carcinomas. *Wien Klin Wochenschr* 2013;125:26–33.
- [6] Tanaka H, Ohira M, Kubo N, et al. Association of location of lymph node metastases with postoperative recurrence of esophageal squamous cell carcinoma. *Anticancer Res* 2012;32:3421–6.
- [7] Feng JF, Zhao Q, Chen QX. Prognostic value of subcarinal lymph node metastasis in patients with esophageal squamous cell carcinoma. *Asian Pac J Cancer Prevent* 2013;14:3183–6.
- [8] Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. *Dis Esophagus* 2009;22:1–8.
- [9] Ferguson MK, Martin TR, Reeder LB, et al. Mortality after esophagectomy: risk factor analysis. *World J Surg* 1997;21:599–603. discussion 603–594.
- [10] Mao WM, Zheng WH, Ling ZQ. Epidemiologic risk factors for esophageal cancer development. *Asian Pac J Cancer Prev* 2011;12: 2461–6.
- [11] Kitajima K, Murakami K, Yamasaki E, et al. Accuracy of 18f-fdg pet/ct in detecting pelvic and paraaortic lymph node metastasis in patients with endometrial cancer. *AJR Am J Roentgenol* 2008;190:1652–8.
- [12] Sohda M, Kato H, Suzuki S, et al. 18f-famtpet is useful for the diagnosis of lymph node metastasis in operable esophageal squamous cell carcinoma. *Ann Surg Oncol* 2010;17:3181–6.
- [13] Hsu PK, Lin KH, Wang SJ, et al. Preoperative positron emission tomography/computed tomography predicts advanced lymph node metastasis in esophageal squamous cell carcinoma patients. *World J Surg* 2011;35:1321–6.
- [14] Toba H, Kondo K, Otsuka H, et al. Diagnosis of the presence of lymph node metastasis and decision of operative indication using fluorodeoxyglucose-positron emission tomography and computed tomography in patients with primary lung cancer. *J Med Invest* 2010;57:305–13.
- [15] Yen TJ, Chung CS, Wu YW, et al. Comparative study between endoscopic ultrasonography and positron emission tomography-computed tomography in staging patients with esophageal squamous cell carcinoma. *Dis Esophagus V* 25 2012;40–7.
- [16] Nini A, Larcher A, Cianflone F, et al. The effect of anatomical location of lymph node metastases on cancer specific survival in patients with clear cell renal cell carcinoma. *Front Surg* 2018;5:26.
- [17] Ikoma N, Estrella JS, Blum M, et al. Central lymph node metastasis in gastric cancer is predictive of survival after preoperative therapy. *J Gastrointest Surg* 2018;22:1325–33.
- [18] Liu J, Hu Y, Xie X, et al. Subcarinal node metastasis in thoracic esophageal squamous cell carcinoma. *Ann Thorac Surg* 2012;93:423–7.
- [19] Lagarde SM, Anderegg MCJ, Gisbertz SS, et al. Lymph node metastases near the celiac trunk should be considered separately from other nodal metastases in patients with cancer of the esophagus or gastroesophageal junction after neoadjuvant treatment and surgery. *J Thorac Dis* 2018;10:1511–21.
- [20] Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2005;23:4330–7.
- [21] Motoori M, Yano M, Ishihara R, et al. Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical t1bn0m0 esophageal cancer. *Ann Surg Oncol* 2012;19:2135–41.
- [22] van Hagen P, Hulshof MC, van Lanschot JJ, et al. Group C. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–84.