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*Original Article*

# Risk factors and prognosis in patients with adenocarcinoma of esophagogastric junction with lymph node metastasis of Siewert II/III

Zhi Zheng[1,2*], Yuxi Shang[3*], Rui Xu[4*], Haiqiao Zhang[1,2*], Jie Yin[1,2], Jun Zhang[1,2], Zhongtao Zhang[1,2]

*[1]Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [2]Beijing Key Laboratory of Cancer Invasion and Metastasis Research & National Clinical Research Center for Digestive Diseases, Beijing, China; [3]Department of Hepatology, Fuxing Hospital, Eighth Clinical Medical College, Capital Medical University, Beijing, China; [4]Department of Pathology, Beijing Friendship Hospital, Capital Medical University, Beijing, China. [*]Equal contributors.*

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**Abstract:** Adenocarcinoma of the esophagogastric junction (AEG) has a high incidence, while the extent of lymph node dissection and prognosis are still controversial. This study aimed to explore the risk factors of lymph node metastasis and prognosis in Siewert II/III AEG patients. Between July 2013 and May 2017, a total of 65 patients who underwent surgical operation in Beijing Friendship Hospital were retrospectively reviewed. The patients were followed up until September 2017. Data were analyzed using logistic regression. Survival analyses were performed using Kaplan-Meier. Multivariate analysis revealed that histologic classification (OR=3.437, 95% CI: 1.046~11.294, P=0.042) and intravascular cancer embolus (OR=6.614, 95% CI: 1.942~22.524, P=0.003) were correlated with lymph node metastasis. The lymph nodes No. 1, 2, 3, 7, 11 and 110 indicated higher metastatic rate. The 3-year overall survival analysis revealed that lymph node metastasis (*P*=0.167) and tumor stage (*P*=0.429) exhibited no significant differences. Findings suggest that histologic type and vascular neoplasia are independent risk factors for lymph node metastasis. For Siewert II/III AEG patients, it is reasonable to perform radical gastrectomy combined with D2 lymph node dissection. For No. 110 lymph nodes should be dissected routinely. However, the long-term prognosis remains to be further studied.

**Keywords:** Adenocarcinoma of esophagogastric junction, Siewert II/III, logistic regression analysis, lymphatic metastasis, survival analysis

## Introduction

Adenocarcinoma of esophagogastric junction (AEG) originates from the glandular epithelium of gastrointestinal tract and invades the esophagogastric junction. In recent years, the incidence and mortality of AEG have increased [1]. This region is a special anatomic location, involving complex functions and multiple lymphatic drainage approaches. The drainage boundary and the extent of lymph node dissection around the stomach, especially for multiple groups of lymph nodes around the cardia are still controversial. Consequently, AEG can be treated with diverse surgical methods, and has a worse prognosis than that of common gastric cancer [2]. Studies have found that posterior mediastinum, paraesophageal and diaphragmatic lymphatic metastasis account for 10%~20% of all lymphatic metastasis [3, 4]. Therefore, it is urgent to increase the lymph node dissection rate in lymph node drainage areas to improve the curative effect of radical operation, improving patient's prognosis. This study aimed to analyze the risk factors and the pattern of lymph node metastasis in Siewert II/III AEG patients. Combined with the results of follow-up data this can provide accurate treatment for AEG patients with different clinicopathologic features.

## Material and methods

### *General information*

A total of 65 Siewert II/III AEG patients undergoing surgical treatment (open or laparoscopic

surgery) between July 2013 and May 2017, with complete clinical data from the General Surgery Department, Beijing Friendship Hospital, were retrospectively studied. Prior to surgery, the patients were diagnosed by routine endoscopy, ultrasound gastroscopy, enhanced CT of abdominal and pelvic cavity as well as pathologic biopsy. They underwent preoperative evaluation of the tumor infiltration depth and lymphatic metastasis. All patients preferred radical gastrectomy in whichno less than 15 lymph nodes were dissected, and did not receive neoadjuvant chemotherapy [5, 6]. All the enrolled patients received a D2 gastrectomy, which is internationally recognized (open or laparoscopic surgery) as standard. All advanced AEG patients also received postoperative adjuvant chemotherapy (XELOX). This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University.

*Inclusion criteria*

(1) Patients who were diagnosed as Siewert type II/III AEG (center of the tumor is located between 1 cm above to 5 cm below the esophagogastric junction) by endoscopy and pathological biopsy. (2) Patients underwent clinical stage evaluation before the surgery, including abdominal enhanced CT and/or ultrasound gastroscopy. (3) The clinical stage was $T_{1\sim4}$ $N_{0\sim3}$ $M_0$ with absence of distant metastasis. In terms of tumor stage, if the tumor invaded the esophagogastric junction, but its center was located at least 2 cm below the esophagogastric junction, or if the tumor did not invade the esophagogastric junction, but its center was located within 2 cm below the esophagogastric junction, the 8$^{th}$ version AJCC/UICC TNM staging system for gastric cancer was adopted. If the tumor invaded the esophagogastric junction, and its center was located within 2 cm below the esophagogastric junction, then the 8$^{th}$ version of the AJCC/UICC TNM stage system for esophageal cancer was adopted [6, 7]. (4) The patients had a physical fitness score, ECOG≤2 points, and were tolerant to D2 gastrectomy. (5) Patients who did not have a previous history of gastrointestinal operation, chemotherapy, or radiotherapy were included in the study.

*Exclusion criteria*

(1) Patients who suffered from gastric remnant carcinoma, recurrent cancer of gastric remnant or multiple primary malignant neoplasm of pelvis or had malignancy history within 5 years. (2) Patients who were unwilling to receive D2 gastrectomy. (3) Patients who were confirmed with metastatic gastric cancer or gastric cancer of other parts intraoperatively. (4) Patients who were confirmed to have non-gastric cancer or have benign gastric tumor by postoperative pathology. (5) Patients who suffered from uncontrollable internal diseases (including unstable angina, myocardial infarction and cerebrovascular accident that occurred within 6 months). (6) Patients who were unable to receive general anesthesia or surgical treatment due to conditions of other organs.

*Observational indicators*

The clinical characteristics and the histopathologic data of the enrolled Siewert II/III AEG patients were recorded, including gender, age, tumor site, tumor size, gross type, histologic classification, infiltrative depth, surgical approach, intravascular cancer embolus, and cancerous node nodules. According to the age groups proposed by the WHO, the patients were divided into an age <60 years group and age ≥60 years group. Tumor size refers to the maximum diameter of the tumors. The gross type was divided into bulging type, flat type, and depressed type according to the Japanese Gastric Cancer Guidelines (2014) [8]. Histologic classification was divided into differentiated type (well-and-moderate differentiated adenocarcinoma, tubular adenocarcinoma) and undifferentiated type (poor differentiated adenocarcinoma, signet-ring cell carcinoma and mucinous adenocarcinoma).

*Follow-up*

The patients were followed up after surgery. After discharge, the patients were followed up by means of outpatient visit, telephone or mail. Follow-up period ended in September 2017.

*Statistical analysis*

Statistical analysis was performed using the SPSS 21.0 software. The count data were ex-

pressed as frequency and percentages, and were compared using the $\chi^2$ test or corrective $\chi^2$ test or Fisher's exact test. Ranked data were expressed as frequency and percentage and were compared using the rank sum test. Multivariate analyses were performed using the logistic regression method. Survival analyses were performed using the Kaplan-Meier and the Log-rank tests. A *P* value less than 0.05 was considered a significant difference.

## Results

### *Baseline data and clinicopathologic characteristics*

A total of 65 Siewert type II/III AEG patients, including 54 men (83.1%) and 11 women (16.9%), with a male to female ratio of 4.9:1 were included in the study. The patient age ranged 42~76 years, and the mean age was 62.3 years. Among a total of 65 patients, 25 patients were <60 years old (38.5%) and 40 patients were ≥60 years old (61.5%). 49 patients suffered from Siewert II AEG, whereas 16 patients suffered from Siewert III AEG. All the patients received curative standard D2 radical gastrectomy. Among them, 41 patients had lymphatic metastasis and the remaining 24 patients did not have lymphatic metastasis. No patients suffered from distant metastasis (**Table 1**).

### *Regulations of lymphatic metastasis*

According to the NCCN guidelines (3rd edition, 2015), lymph node groups No. 1, 2, 3, 7 and 11 had higher rate of metastasis in the 65 AEG patients, with the metastatic rates of 45.3%, 32.5%, 28.8%, 22.5%, and 19.4%, respectively. This was followed by groups No. 19 and No. 9 lymph node metastasis, with metastatic rates of 14.3% and 12.1%, respectively (**Table 2**). Among them, type II AEG was prone to metastasize to No. 110, with a metastatic rate of 8.2%, while mediastinal lymph node metastasis was not found in 16 patients with type III AEG. No metastases to groups No. 111 and No. 112 lymph nodes were found in the AEG patients (**Table 3**).

### *Univariate analysis*

Among the 65 Siewert II/III AEG patients included in this study, 41 patients suffered from lymph node metastasis with a metastatic rate of 63.1%. Of these, the metastatic rates were 0 and 71.9% in patients with tumor sizes of <2 cm and ≥2 cm, respectively. This suggested that patients with a tumor size of ≥2 cm were more prone to peripheral lymph node metastasis (*P*=0.000). In addition, the lymph node metastatic rate in patients with differentiated tumors was 45.2%, which was lower than that of 79.4% in patients with undifferentiated tumors (*P*=0.009), and it was elevated with an increased tumor infiltration depth (*P*=0.000). The lymph node metastasis rate in patients with intravascular cancer embolus and without intravascular cancer embolus were 40.6% and 84.8%, respectively (*P*=0.001). All the differences were statistically significant (**Table 1**). However, patient age, gender, tumor site, gross type, surgical approach and cancerous nodules were not correlated with lymph node metastasis (**Table 1**).

### *Multivariate analysis*

As shown in **Table 2**, the histologic classification and intravascular cancer embolus were independent risk factors for lymph node metastasis in II/III AEG patients. The risk of undifferentiated tumors associated with lymph node metastasis was 3.437 times that of the differentiated tumors (95% CI: 1.046~11.294), and the risk of lymph node metastasis in patients with intravascular cancer embolus was 6.614 times that of patients without intravascular cancer embolus (95% CI: 1.942~22.524), (**Table 4**).

### *Follow-up and survival analysis*

All the patients were followed up for 1-45 months (median duration of 18.81 months), with a follow-up rate of 100%. Of these patients, 14 patients were followed up for 3 years. During the follow-up period, 9 patients died from postoperative complications, recurrence, or distant metastasis. The 3-year overall survivals (OS) of the AEG patients without lymph node metastasis (4 cases) and with lymph node metastasis (10 cases) were respectively 100% and 60% (*P*=0.167, **Figure 1**). According to the AJCC/UICC TNM staging criteria (8th edition) [6, 7], the 3-year OS indicated no differences among stage I (14 cases), II (17 cases), and III (34 cases) patients ($X^2$=3.836; *P*=0.429, **Figure 2**), but the survival in patients

**Table 1.** Correlation between clinicopathologic factors and lymphatic metastasis in 65 cases of Siewert type II/III AEG

| Clinicopathologic factor | Number of cases | Lymphatic metastasis [n (%)] | No lymphatic metastasis [n (%)] | *P* value |
|---|---|---|---|---|
| Age | | | | 0.887 |
| <60 | 25 | 15 (60) | 10 (40) | |
| ≥60 | 40 | 26 (65) | 14 (35) | |
| Gender | | | | 0.324 |
| M | 54 | 36 (66.7) | 18 (33.3) | |
| F | 11 | 5 (45.5) | 6 (54.5) | |
| Tumor site | | | | 0.956 |
| Siewer II | 49 | 31 (63.3) | 18 (36.7) | |
| Siewert III | 16 | 10 (62.5) | 6 (37.5) | |
| Tumor size | | | | 0.000 |
| <2 cm | 8 | 0 (0) | 8 (100) | |
| ≥2 cm | 57 | 41 (71.9) | 16 (28.1) | |
| Gross type | | | | 0.164 |
| Bulging | 8 | 4 (50) | 4 (50) | |
| Flat | 4 | 1 (25) | 3 (75) | |
| Depressed | 53 | 36 (67.9) | 17 (32.1) | |
| Surgical approach | | | | 0.838 |
| Proximal gastrectomy | 22 | 13 (59.1) | 9 (40.9) | |
| Total gastrectomy | 43 | 28 (65.1) | 15 (34.9) | |
| Infiltration depth | | | | 0.000 |
| $T_1$ | 7 | 0 (0.0) | 7 (100) | |
| $T_2$ | 8 | 1 (12.5) | 7 (0.875) | |
| $T_3$ | 29 | 20 (69.0) | 9 (31.0) | |
| $T_4$ | 21 | 20 (95.2) | 1 (4.8) | |
| Histologic classification | | | | 0.009 |
| Differentiated | 31 | 14 (45.2) | 17 (54.8) | |
| Undifferentiated | 34 | 27 (79.4) | 7 (20.6) | |
| Intravascular cancer embolus | | | | 0.001 |
| Negative | 32 | 13 (40.6) | 19 (59.4) | |
| Positive | 33 | 28 (84.8) | 5 (15.2) | |
| Cancerous nodule | | | | 0.448 |
| Negative | 63 | 40 (63.5) | 23 (36.5) | |
| Positive | 2 | 1 (50.0) | 1 (50.0) | |

with early stage tumors was better than that in patients with advanced stage tumors. This suggests that although patients with advanced stage tumors received postoperative adjuvant chemotherapy, their prognosis may still be worse than patients with early stage tumors.

## Discussion

In this study, the lymph node metastasis characteristics as well as short-term and long-term prognosis in 65 adenocarcinoma of esophagogastric junction (AEG) patients were retrospectively analyzed in order to explore the risk factors and the prognosis of Siewert II/III AEG. Multivariate analysis suggested that the histologic classification and the intravascular cancer embolus were independent risk factors for lymph node metastasis of Siewert II/III AEG. The lymph node metastasis rate was highest in groups No. 1, 2, 3, 7, 11 and 110. Survival analysis revealed that lymph node metastasis and tumor stage showed no significant difference in the 3-year OS analysis. However, the

**Table 2.** Abdominal lymph node metastasis rate

| Lymph node group | Lymph node metastasis rate (%, n/N) |
|---|---|
| No. 1 | 45.3 (24/53) |
| No. 2 | 32.5 (13/40) |
| No. 3 | 28.8 (15/52) |
| No. 4 | 9.30 (4/43) |
| No. 5 | 5.13 (2/39) |
| No. 6 | 5.71 (2/35) |
| No. 7 | 22.5 (9/40) |
| No. 8 | 8.2 (4/49) |
| No. 9 | 12.1 (4/33) |
| No. 10 | 6.67 (1/15) |
| No. 11 | 19.4 (7/36) |
| No. 12 | 0 (0/31) |
| No. 19 | 14.3 (1/7) |
| No. 20 | 0 (0/11) |

**Table 3.** Mediastinal lymph node metastatic rate in patients with Siewert II/III AEG

| Lymph node group | Siewert II (%, n/N) | Siewert III (%, n/N) |
|---|---|---|
| No. 110 | 8.2 (4/49) | 0 (0/16) |
| No. 111 | 0 (0/49) | 0 (0/16) |
| No. 112 | 0 (0/49) | 0 (0/16) |

patients with stage I tumors might have a better survival rate than patients with advanced stage tumors. Lymph node metastasis is one of the important factors that affect the prognosis and surgical approach in Siewert II/III AEG patients [9]. Therefore, how to reasonably determine the extent of lymph node dissection to effectively improve the postoperative survival time, and reduce postoperative complications and mortality as well as decrease patient suffering has gradually became the focus of general surgeons. Radical surgery is still the preferred treatment for AEG, including complete resection of lesions and regional lymph node dissection. This is true because of the special anatomic location of II/III AEG, the tumor infiltration depth, and the complex lymphatic drainage structure [10]. Thus, how to correctly assess the lymph node metastasis, how to determine the extent of optimal lymph node dissection, and how to develop a reasonable treatment protocol are of great significance for improving the long-term prognosis in lymphatic metastasis patients with II/III AEG.

For the AEG patients, how to select a more rational surgical approach depends on the preoperative assessment of histologic classification and lymph node metastasis. Preoperatively, ultrasound gastroscopy and enhanced CT can be used to determine the lymph node metastasis, followed by endoscopic pathologic biopsy. Based on these results, lymph node metastasis can be evaluated for selection of optimal surgical approach.

In terms of the histologic classification, the degree of tumor differentiation determines its biological characteristics. The worse the cell differentiation, the higher the probability of lymph node metastasis. In this study, among the 34 undifferentiated AEG patients, 27 patients (79.4%) had lymph node metastasis. The difference was significant compared to differentiated AEG. Thiswas consistent with the results which reported by Hiroaki [11]. Because the tumor cells with poor differentiation present a large heterogeneity and a strong invasiveness, and thus were prone to lymph node metastasis. In addition, among the 33 patients who were combined with intravascular cancer embolus, 28 patients suffered from lymph node metastasis, an incidence that was significantly higher than those who did not have intravascular cancer embolus. Ti YX et al. [12] studied 54 gastric cancer patients with intravascular cancer embolus, and found that 51 patients had lymph node metastasis (94.4%). This may be due to the capillary wall does not have basal membrane, and was composed of endothelial cells, where most of these were imbricately arranged. Therefore, the capillary wall had greater permeability than the capillary, and was more susceptible to cancer cell invasion. Nevertheless, since it was difficult to determine whether patients were combined with intravascular cancer embolus preoperatively, histological classification and tumor infiltration depth remained more valuable indicators.

Lymph node metastasis is one of the important factors which affected the prognosis of AEG patients. Wang [13] analyzed 248 AEG patients, and found that the postoperative OS were 64 months. The 1-year, 3-year, and 5-year survival rates were 80.4%, 60.8%, and 51%, respectively. Cox regression analysis revealed that the number of lymph nodes dissected and tumor invasion depth were independent prog-

**Table 4.** Multivariate analysis results for risk factors of lymph node metastasis in type II/III AEG patients

| Index | B | S.E | Walds | P | OR | 95% *CI* |
|---|---|---|---|---|---|---|
| Histologic classification | 1.235 | 0.607 | 4.136 | 0.042 | 3.437 | 1.046~11.294 |
| Intravascular cancer embolus | 1.899 | 0.625 | 9.132 | 0.003 | 6.614 | 1.942~22.524 |

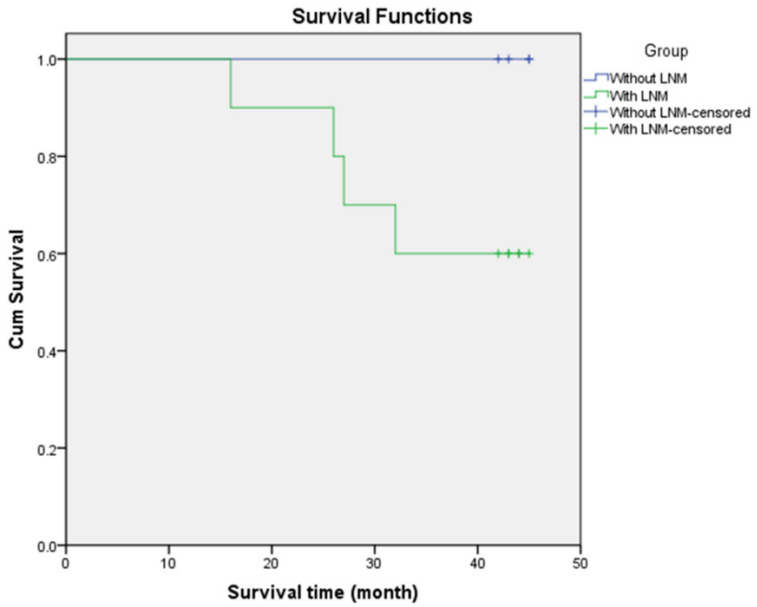


**Figure 1.** Postoperative 3-year overall survival analysis of AEG.

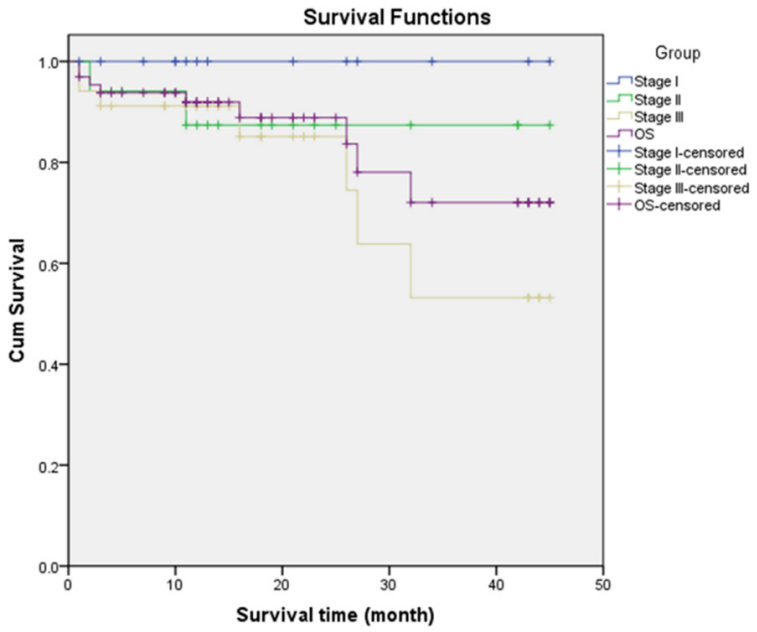


**Figure 2.** Postoperative 3-year overall survival in patients with different stages of II/III AEG.

nostic factors. It found that the patients with small numbers of lymph node metastases had a better prognosis compared with patients with a large number of lymph node metastases. Patients with $T_1$ stage who had >10 lymph nodes dissected had a better prognosis compared to those patients with $T_2$~$T_3$ stage who had >15 nodes dissected [14]. Therefore, we believe that lymph nodes should be detected as much as possible in order to obtain an accurate tumor stage. Also, the long-term prognosis was associated with degree of tumor differentiation and with whether or not to undertake radical resection. Some scholars believe that age was also one of the independent factors for determining the long-term prognosis of patients [15]. In this study, the patients were followed up from 1 month to 45 months. The mean follow-up time was 18.81 months. During the follow-up period, 9 patients died from postoperative complications, recurrence or distant metastasis, while the long-term prognosis indicated no significant difference between the patients with and without lymph node metastasis. Furthermore, although the patients with different tumor stages showed no significant difference in long-term prognosis, survival analysis revealed that the survival of patients with stage I was superior to that of the patients with advanced stages. This is

consistent with the National Comprehensive Cancer Network (NCCN) and Japan Gastric Cancer Guidelines. These outcomes may bedue to the small sample size of the present study, and need to be confirmed in larger sample size clinical trials. We believe that the long-term prognosis of the AEG patients may be associated with tumor stage, lymph node metastasis, complications, and whether to receive radical operation.

Due to the special anatomic location of the esophagogastric junction, it is prone to lymph node metastasis in the mediastinal and abdominal cavities. Thus, we recommend that regional lymph node dissection be according to the characteristics of lymph node metastasis in different subtypes of AEG. The II/III AEG lymph node drainage is dominated by abdominal lymph node metastasis [16]. Among the 65 AEG patients, the lymph node metastasis rate was highest in No. 1, 2, 3, 7 and 11 lymph nodes, followed by No. 19 and 9 lymph nodes. The mediastinal lymph nodes mainly metastasized in group No. 110 lymph nodes which need to be dissected. However, since it is difficult to identify the extent of No. 19, 20, 110, 111 and 112 lymph nodes, we recommend dissection of the lymph nodes that surround the esophageal hiatus and inferior mediastinum in order to reduce tumor residue. Intraoperatively, we need to perform a standard lymph node dissection while arbitrarily expanding or narrowing the dissection extent should be prohibited. Moreover, we should emphasize to favor radical resection, and avoid fragmented resection. It is better to remove lymph nodes as much as possible. After lymph node dissection, we should evaluate whether normative resection has been achieved, and perform additional lymph node dissection if necessary [9, 17].

In terms of limitations, this is a retrospective, single-center study involving a small number of samples, and patients were followed-up for a short time. Thus, the results are unlikely to fully reflect the pattern of lymph node metastasis and long-term prognosis. All the results need to be studied by large-sample, randomized controlled studies.

In summary, lymph node metastasis was mainly associated with histologic classification and intravascular cancer embolus. Lymph node groups No. 1, 2, 3, 7, 11 and 110 showed a high metastatic rate. It is reasonable to perform radical gastrectomy with D2 lymph node dissection. The lymph nodes of group No. 110 and esophageal hiatus were need to be dissected routinely. For advanced stage patients with lymph node metastasis, the long-term prognosis may be even worse. However, all the results remain to be verified through large-sample, multi-center, randomized controlled studies.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Jun Zhang, Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, 95 Yong-An Road, Xi-Cheng District, Beijing 10050, China. E-mail: zhangjun5986@ccmu.edu.cn

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