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Study on Risk Factors and Prognosis of Lymph Node Metastasis of Siewert II/III Adenocarcinoma of Esophagogastric Junction

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Abstract

Purpose: This study aimed to explore the risk factors and prognosis of lymph node metastasis in patients with Siewert II/III AEG.

Methods and Materials: 65 Siewert II/III AEG patients undergoing surgical treatment (open or laparoscopic surgery) from July 2013 to May 2017, with complete clinical data from Beijing Friendship Hospital were included in the study. Patients were followed up until September 2017.

Results: Multivariate analysis revealed that histological 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. Lymph nodes No. 1, 2, 3, 7, 11 and 110 groups showed a high lymph node metastatic rate. The 3-year overall survival analysis revealed that lymph node metastasis (P=0.167) and tumor staging (P=0.429) showed no significant differences.

Conclusion: Histological type and vascular neoplasia are risk factors of lymph node metastasis. For Siewert II/III AEG patients, radical total gastrectomy combined with D2 lymphatic nodes dissection was suggested, No. 110 lymph nodes should be also 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

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Introduction

In recent years, the incidence and mortality of Adenocarcinoma of Esophagogastric junction (AEG) are increasing [1]. Due to the special anatomical location, AEG involves complex operation and multiple lymphatic drainage approaches. The drainage boundary and dissection extent of lymph nodes around the stomach, especially for multiple groups of lymph nodes around the cardia, such as periesophageal hiatus and inferior mediastinum regions, are still controversial, resulting in diverse and poorly normative surgical methods, as well as poorer prognosis than that of normal gastric cancer [2]. Studies have found that posterior mediastinum, paraesophageal and diaphragmatic lymphatic metastasis accounts 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 the prognosis of the disease. This study attempted to analyze the risk factors and metastatic regulation of lymphatic metastasis in patients. Results of the combined follow-up survival data tended to provide a basis for developing more accurate treatment for AEG patients with different clinicopathological features.

Methods

General information

Between July 2013 and May 2017, a total of 65 Siewert II/III AEG patients undergoing surgical treatment (open or laparoscopic surgery), with complete clinical data from our hospital were retrospectively studied. This study gained approval from the Ethics committee of our hospital. The need for individual consent was waived because of the retrospective nature of the study. Before surgery, all patients were diagnosed by endoscopy, ultrasound gastroscope, enhanced CT of abdominal and pelvic cavity as well as pathologic biopsy. Also underwent preoperative evaluation of tumor infiltration depth and lymphatic metastasis. If the perioperative clinical stage is $cT_{3-4}N_{+}M_{0}$, patients will receive three cycle neoadjuvant chemotherapy (XELOX) firstly. Then, all the enrolled

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

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

patients were performed standard D2 radical resection for gastric cancer (open or laparoscopic surgery) and no less than 15 lymph nodes were dissected [5,6]. Finally, patients with advanced AEG were given total six cycle adjuvant chemotherapy (XELOX) as standard treatment postoperatively.

Inclusion criteria

(1) Patients who were diagnosed as Siewert II/III AEG by endoscopy and pathologic biopsy. (2) Patients underwent clinical staging diagnosis before the surgery. (3) Patients had a clinical stage of $cT_{1\sim4}N_{0\sim3}M_0$, with absence of distant metastasis. In terms of tumor staging, 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 8th version AJCC/UICCTNM 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 8th version of AJCC/UICCTNM staging system for esophageal cancer was adopted [6,7]. (4) Patients had a physical fitness score, ECOG ≤ 2 points, and were tolerant to D2 lymph node dissection. (5) Patients did not have previous history of gastrointestinal operation, chemotherapy or radiotherapy.

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 undergo D2 lymph node dissection. (3) Patients who were confirmed with metastatic gastric cancer or gastric cancer of other parts intraoperatively. (4) Patients who suffered from uncontrollable internal diseases (including unstable

angina, myocardial infarction and cerebrovascular accident that occurred within 6 months). (5) Patients who were unable to receive general anesthesia or surgical treatment due to conditions of other organs.

Observatory indicators

Clinical characteristics and histopathological data were recorded, including gender, age, tumor site, tumor size, gross type, histological classification, infiltration depth, surgical approach, intravascular cancer embolus, cancerous node nodules. According to the age group proposed by WHO, patients were divided into age <60 years group and age ≥ 60 years group. Tumor size was referred to the maximum diameter of the tumors. The gross type was divided into bulged type, flat type and depressed type according to the Japan Gastric Cancer Regulations (2014) [8]. Histological classification was divided into differentiated type (well-and-moderate differentiated adenocarcinoma, tubular adenocarcinoma and mucinous adenocarcinoma) and undifferentiated type (poor differentiated adenocarcinoma, signet-ring cell carcinoma and neuroendocrine carcinoma).

Follow-up

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

Statistical analysis

Statistical analyses were performed using SPSS 21.0 software. The count data were expressed as frequency and percentage, and were compared using χ^2 test or corrective χ^2 test or Fisher's exact test. Ranked data were expressed as frequency and percentage and were compared using rank sum test. Multivariate analyses were performed using Logistic regression method. Survival analyses were performed using Kaplan-Meier and Log-rank tests. A difference of P<0.05 was considered statistically significant.

Results

Baseline data and clinicopathological characteristics

65 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. Patients' age ranged 42~76 years, and with a mean age of 62.3 years. Of the 65 patients, 25 cases were <60 years old (38.5%) and 40 cases were ≥ 60 years old (61.5%). Forty nine patients suffered from Siewert II AEG, and 16 patients suffered from Siewert III AEG. There are 40 patients whose clinical stage is $cT_{3-4}N_{+}M_{0}$ receive three cycle neoadjuvant chemotherapy (XELOX) firstly. Then, all the patients underwent curative standard D2 radical gastrectomy. Among them, 41 cases were combined with lymphatic metastasis and the rest 24 cases did not undergo lymphatic metastasis. No cases suffered from distant metastasis. Finally, 51 patients with advanced AEG ($T_{2-4}N_{any}M_{0}$) were given six cycle adjuvant chemotherapy (XELOX) as standard treatment postoperatively (Table 1).

Regulations of lymphatic metastasis

According to the NCCN guidelines (3rd edition, 2015), No.1, 2, 3, 7 and 11 lymph node metastases were found 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 No.19 and No.9 lymph node metastases, with the metastatic rates of 14.3% and 12.1%, respectively (Table 2). Among them, in patients with mediastinal lymph nodes, 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 cases of type III AEG. Positive metastatic lymph nodes were not found in No. 111 and 112 (Table 3).

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 grouping	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)

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

Univariate analysis

Among the 65 patients in this study, 41 cases 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 a tumor size of <2 cm and ≥ 2 cm, respectively. This meant that patients with a tumor size of ≥ 2 cm are 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 the increased tumor infiltration depth (P=0.000). The lymph node metastatic rates 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. However, age, gender, tumor site, gross type, surgical approach and cancerous nodules were insignificantly correlated with lymph node metastasis (Table 1).

Multivariate analysis

As shown in Table 4, the histological classification and intravascular cancer embolus were independent risk factors of lymph node metastasis in type II/III AEG patients. The risk of undifferentiated tumors associated with lymph node metastasis was 3.437 times that of differentiated tumors (95% CI: 1.046 ~ 11.294),

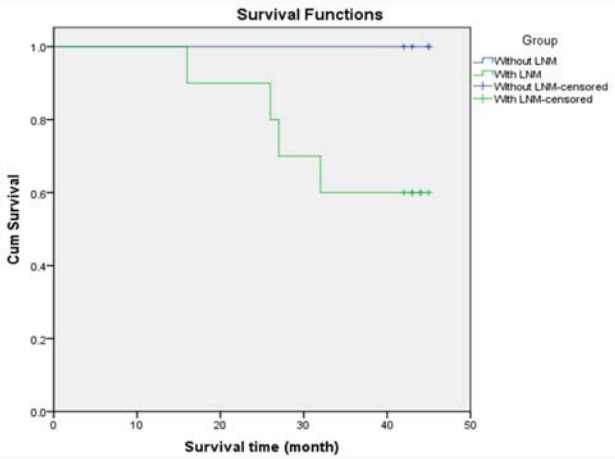

Figure 1: Postoperative 3-year overall survival analysis of AEG.

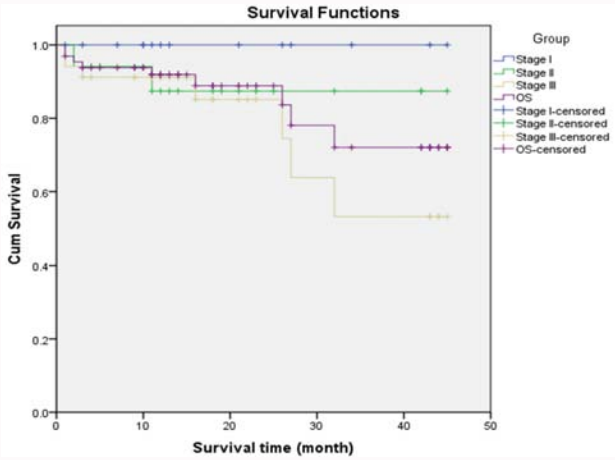

Figure 2: Postoperative 3-year overall survival in patients with different stages of II/III AEG.

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).

Follow-up and survival analysis

In this study, all the 65 patients were followed up for 1-45 months (median duration of 18.81 months), with a follow-up rate of 100%. Of these, 14 cases were followed up for 3 years. During the follow-up period, 9 cases died of postoperative complications, recurrence or distant metastasis. Of which, the 3-year Overall Survival (OS) of AEG patients who were not accompanied by lymph node metastasis (4 cases) and accompanied by lymph node metastasis (10 cases) were respectively 100% and 60%, where the difference was statistically insignificant (P=0.167, Figure 1). According to the AJCC/UICCTNM staging criteria (8th edition) [6,7], the 3-year OS showed no significant differences among stage I (14 cases), II (17 cases) and III (34 cases) patients (X^2=3.836; P=0.429, Figure 2), though the patients with stage II and III received adjuvant chemotherapy (XELOX) after surgery. We find that the survival in patients with early tumors was better than that in patients with advanced tumors. This suggested that although patients with advanced tumors are given neoadjuvant chemotherapy (XELOX) before surgery and standard adjuvant chemotherapy after surgery, their prognosis may still be worse than that of patients with early tumors.

Discussion

Lymph node metastasis is one of the important factors affecting the prognosis and surgical approach in patients with Siewert II/III AEG [9]. Therefore, how to reasonably select the extent of lymph node dissection to more effectively improve the postoperative survival time, reduce postoperative complications and mortality as well as shorten the suffering in patients has gradually become the focus of General Surgeons. Radical surgery is still the preferred treatment for AEG, including complete resection of lesions and regional lymph node dissection [10].

For patients with type II/III AEG, how to select a more rational surgical approach depends on the preoperative assessment of histological classification and lymph node metastasis. In terms of histological classification, the degree of tumor differentiation determines its biological characteristics. The worse is the cell differentiation, the higher the probability of lymph node metastasis. In this study, among the 34 cases with undifferentiated AEG, 27 cases (79.4%) were combined with lymph node metastasis, where the difference was significantly compared with those of differentiated AEG. This was in consistent with the results reported by Hiroaki [11]. This is because the tumor cells with poor differentiation present a large heterogeneity and a strong invasiveness, and thus are more prone to lymph node metastasis. In addition, among the 33 cases who were combined with intravascular cancer embolus, 28 cases suffered from lymph node metastasis, where the incidence was significantly higher than those who were not combined with intravascular cancer embolus? TI YX et al. [12] studied 54 gastric cancer patients with intravascular cancer embolus, and found that 51 cases had lymph node metastasis (94.4%). This may be because the capillary wall does not have basal membrane, and is composed of endothelial cells, where most of these are imbricately arranged. Therefore, the capillary wall has greater permeability than the capillary, and is more susceptible to cancer cell invasion. Nevertheless, since it is difficult to determine whether patients are combined with intravascular cancer embolus preoperatively, histological classification and tumor infiltration depth remain more valuable indicators. Lymph node metastasis is one of the important factors affecting the prognosis of AEG patients. Wang et al. [13] analyzed lymph node metastasis in 248 AEG patients, and found that the postoperative OS was 64 months, where the 1-year, 3-year and 5-year survival rates were 80.4%, 60.8% and 51%, respectively. Cox regression analysis revealed that lymph node dissection number and tumor invasion depth were independent prognostic factors. It has been found that patients with greater number of lymph node metastasis have a worse prognosis compared with patients of small number of lymph node metastasis. While patients with T1 tumor who have lymph node dissection number >10 have a better prognosis compared with those with T2 ~ T3 tumor who have a lymph node dissection number >15 [14]. Therefore, we believe that in order to obtain accurate staging, lymph nodes should be detected as much as possible. Besides, the postoperative long-term survival time is also associated whether to achieve radical resection and degree of tumor differentiation. Some scholars believe that age was also one of the independent factors for determining the long-term prognosis of patients [15]. In this study, patients were followed up for 1 ~ 45 months, with a median duration time of 18.81 months. During the follow-up period, 9 cases died of postoperative complications, recurrence or distant metastasis, while

the long-term prognosis showed no significant difference between patients with and without a combination of lymph node metastasis. Furthermore, although patients with different tumor staging showed no significant difference in long-term prognosis, survival analysis revealed that survival of patients with stage I tumors was superior to that of patients with advanced tumors. This was in consistent with the National Comprehensive Cancer Network (NCCN) and Japan Gastric Cancer Guidelines. These results may be related to the small sample size of this study, and are subject to confirmation in studies with larger sample size. We believe that the long-term survival time of II/III AEG patients may be associated with tumor staging, lymph node metastasis, complications and whether to undergo radical resection. Due to the special anatomical location of esophagogastric junction, it was more prone to mediastinal and abdominal lymph node metastasis. Thus, we recommend regional lymph node dissection according to the characteristics of lymph node metastasis in different subtypes of AEG. Of which, the type II/III AEG lymph node drainage was dominated by abdominal lymph node metastasis [16]. Among the 65 AEG patients, the lymph node metastatic rate was highest in lymph nodes No. 1, 2, 3, 7 and 11 groups, followed by No. 19 and 9 groups. The mediastinal lymph nodes were mainly metastasized at No.110 group, where routine dissection should be conducted. However, since it is difficult to identify the extent of No. 19, 20, 110, 111 and 112 groups, we recommend dissection of the lymph nodes that surround the esophageal hiatus and in the inferior mediastinum to reduce tumor cell residues. The extent of medaistinal lymphadenectomy should reach the lower pulmonary vein, mediastinal pleura and pericardium. Intraoperatively, anatomy should be strictly analyzed according to the standard extent of lymph node dissection, while arbitrarily expanding or narrowing the dissection extent should be prohibited. Moreover, we should emphasize on radical resection, and avoid fragmented resection, removal or direct incision of lymph node as much as possible. After lymph node dissection, we should confirm whether standardized and normative resection has been achieved in the important regions, and perform additional lymph node dissection if necessary [9,17]. In terms of limitations, this is a retrospective, single-center study, involving only a small number of patients are followed up for shorter duration. The results are unlikely to fully reflect the regulation of lymph node metastasis and long-term prognosis. Thus, we need to be further confirmed by large-sample, randomized controlled studies. In summary, histological type and vascular neoplasia are risk factors of lymph node metastasis. Of which, lymph nodes No. 1, 2, 3, 7, 11 and 110 groups showed a high metastatic rate. For these patients, radical total gastrectomy combined with D2 lymphatic nodes dissection was suggested, No. 110 lymph nodes should be also dissected routinely. However, the long-term prognosis remains to be further studied.

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Trial Registration

ClinicalTrials.gov Identifier: NCT01441336.

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