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Explored Risk Factors for Lymph Node Metastasis with Siewert II/III Adenocarcinoma of the Gastroesophageal Junction

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Abstract. *Aim: To explore the risk factors and prognosis for lymphatic metastasis (LNM) in patients with Siewert II/III adenocarcinoma of the gastroesophageal junction (AEG). Patients and Methods: This study retrospectively reviewed 49 patients with Siewert II/III AEG. Clinical characteristics and pathological features were analyzed by the Chi-square the and binary logistic regression. Survival data were analyzed using the Kaplan–Meier method. Results: LNM frequency was found in lymph nodes No.1, No.2, No.3, No.7, No.11 and No.110. The results revealed that depth of infiltration, neoplasms by histological type and lymphatic embolus were independent risk factors for LNM. The 1- and 3-year survival of patients without LNM were both 100%, while patients with LNM had 70% and 60% survival, respectively. Although the differences were not statistically significant, survival rate with negative lymph nodes was higher than in patients with LNM. Conclusion: Total gastrectomy combined with D2 No.110 lymphadenectomy might improve the prognosis for LNM patients.*

The incidence of adenocarcinoma of the esophagogastric junction (AEG) has rapidly increased in Western and Eastern countries over the past decades (1). Meanwhile, AEG is commonly regarded as a separate tumor entirety of digestive tract cancer (2, 3). AGE is a malignant tumor with early hematogenous and lymphatic dissemination. Despite use of chemotherapy, the 5-year survival rate has been reported to be below 30% for AEG (4, 5). Surgery remains a mainstay and optimal surgical method for treating patients with AEG and is of considerable interest (6, 7). Siewert types have been widely accepted; type I is defined as tumors with the epicenter located 1-5 cm above the esophagogastric junction (EGJ) regardless of the invasion to the EGJ, type II as tumors that invade the EGJ with the epicenter located between 1 cm above and 2 cm below the EGJ and type III as tumors that invade the EGJ with the epicenter located 2-5 cm below the EGJ (7).

Since the biological behavior of AEGs is different according to tumor location, and in particular the regulation of lymph node metastasis, AEGs can metastasize to both thoracic and abdominal cavities. In such a case, surgical procedures, as well as the extent of lymphadenectomy, are controversial (8, 9). In recent years, due to minimal trauma and rapid recovery, precision medical treatment has generally been accepted as the best method to improve the quality of life for AEG patients (10). Therefore, we aimed to clarify the related risk factors and prognosis for lymphatic metastasis in patients with Siewert II/III AEG in order to provide theoretical evidence for establishing a reasonable therapeutic schedule.

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Key Words: Adenocarcinoma of the gastroesophageal junction, Siewert II/III, univariate analysis, logistic regression analysis, lymphatic metastasis.

Patients and Methods

General information. This study retrospectively reviewed 49 patients who underwent radical surgery (open or laparoscopic) for Siewert II/III AEG in the Beijing Friendship Hospital from July 2013 to July 2016. Complete clinical data were available for all patients. Among the 49 AEG patients, 43 (87.8%) patients were male and 6 (12.2%) female with a male-to-female ratio of 7.2:1. The age of patients ranged from 40 to 76 years with a median age of 61.6. Furthermore, among these patients, 21 (42.9%) were <60 years old, while 28 (57.1%) were ≥60 years old. Gastroscopy, abdominal and pelvic enhanced computed tomography (CT), electronic ultrasonic gastroscopy and biopsies were performed on all Siewert II/III AEG patients before surgery for preliminary staging. All patients who underwent R0 resection cleared away ≥15 lymph nodes. Due to bias that may have occurred in our preoperative staging, all patients enrolled in this study underwent D2 lymphadenectomy. The study was approved by the Ethics Review

Board of Beijing Friendship Hospital and written informed consent was obtained from each participant.

Analysis of clinical outcome. The following postoperative clinicopathological parameters were evaluated: gender, age, tumor location in the stomach (Siewert II and Siewert III), tumor size (<2 cm or ≥2 cm), macroscopic type (elevated, flat and depressed type), histological classification (differentiated and undifferentiated), depth of infiltration (T1 and T2-T4), operation type (proximal gastrectomy and total gastrectomy), lymphatic invasion, carcinoma nodes, distant metastasis, as well as 1- and 3-year survival. Following the criteria of the World Health Organization (WHO) classification for age, patients were divided into two groups: patients <60 years old and ≥60 years old. The macroscopic appearance of AEG was analyzed in accordance with the Japan Classification of Gastric Cancer (2014.ver 4). Tumor histology was classified into two groups: (a) differentiated, which included well- or moderately differentiated adenocarcinomas and tubular adenocarcinomas; (b) undifferentiated, which included poorly differentiated, signet ring cell carcinomas and mucinous adenocarcinomas.

Statistical analysis. All data were analyzed by IBM SPSS 21.0 (https://www.ibm.com/analytics/us/en/technology/spss/). Univariate and multivariate analyses of risk factors associated with LNM were conducted using the χ^2 test and logistic regression models, respectively. Survival data of operated patients were analyzed using the Kaplan-Meier method, while log-rank test was used to assess differences between prognostic factors. All $p<0.05$ values were considered statistically significant.

Results

Clinical features of patients. Table I summarizes the clinicopathological characteristics of patients in relation to the presence of LNM. Among the 49 AEG patients, tumor was found in Siewert II in 36 (73.5%) patients and Siewert III in 13 (26.5%) patients. Furthermore, 5 patients (10.2%) were found to have a tumor <2.0 cm in size, while 44 (89.8%) patients had a tumor ≥2.0 cm in size. Elevated-type tumors were macroscopically observed in 5 (10.2%) patients, flat-type tumors in 4 (8.2%) and depressed-type tumors in 40 (81.6%). All patients enrolled in this study underwent D2 lymphadenectomy. Among them, proximal gastrectomy and total gastrectomy were performed in 18 (36.7%) and 31 (63.3%) patients, respectively. Based on the degree of anaplasia, 4 (8.2%) patients had well-differentiated adenocarcinomas, 3 (6.1%) well-moderately differentiated adenocarcinomas, 17 (34.7%) moderately differentiated adenocarcinomas, 3 (6.1%) moderate-poorly differentiated adenocarcinomas, 18 (36.7%) poorly differentiated adenocarcinomas and 4 (8.2%) signet ring cell carcinomas. In total, 24 (49%) patients were differentiated, while 25 (51%) patients were undifferentiated. AEG was limited to T1 in 4 (8.2%) patients, while it infiltrated T2-T4 in 45 (91.8%) patients. Twenty-four patients (49%) had lymphatic invasion and one patient (2.0%) carcinoma nodes. None of the patients had distant metastasis.

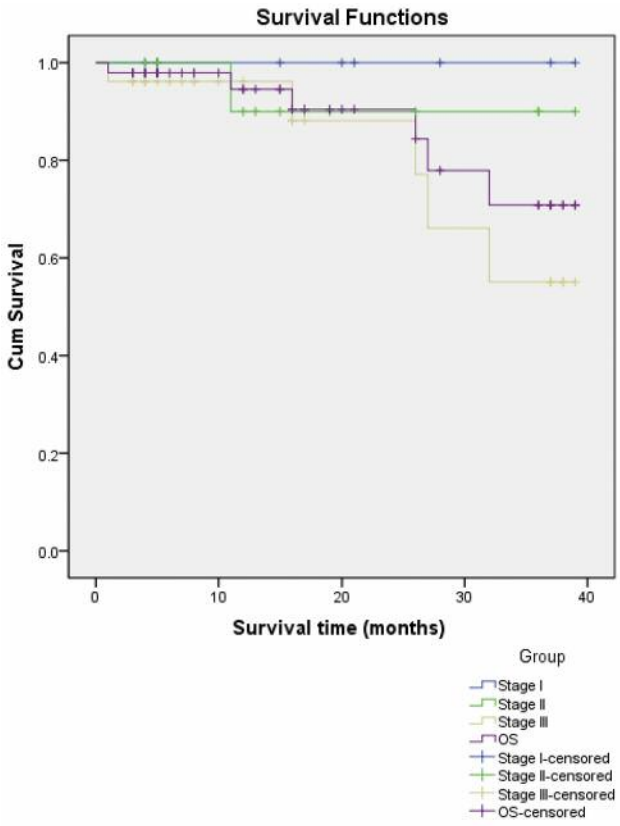

Figure 1. *Analysis of overall survival (OS) rates. One- and 3-year OS rates were 93.5% (29/31) and 71.4% (10/14), respectively. Median survival time was 24.1 months (range=1-39).*

Lymph node metastasis condition. According to National Comprehensive Cancer Network (NCCN) clinical practice guidelines (2015.V3), among patients, lymph nodes No. 1, 2, 3, 7 and 11 had a higher metastatic rate than others (48.6%, 42.7%, 31.6%, 22.6% and 17.9%, respectively) (Table II). Among the patients with mediastinal lymph node metastasis, the rate of No. 110 lymph node metastasis was 8.3% (Table III). None of the patients enrolled in this study underwent D3 lymphadenectomy.

Univariate analysis results. Among the 49 AEG patients included in the analysis, LNM was observed in 32 of 49 patients, with the metastatic rate being 65.3%. The metastatic rate of patients with tumor size <2 cm was 0% (0/5), while the rate for patients with tumor size ≥2 cm was 72.7% (32/44) ($p=0.001$). Therefore, patients with tumor size ≥2 cm were more likely to develop LNM. The observed rate of LNM was 0% (0/4), 0% (0/5), 68.2% (15/22) 94.4% (17/18) in T1, T2, T3 and T4 ($p=0.000$), respectively. The metastatic rate of highly differentiated AEGs was (50%, 12/24) lower compared with poorly differentiated tumors (80%, 20/25)

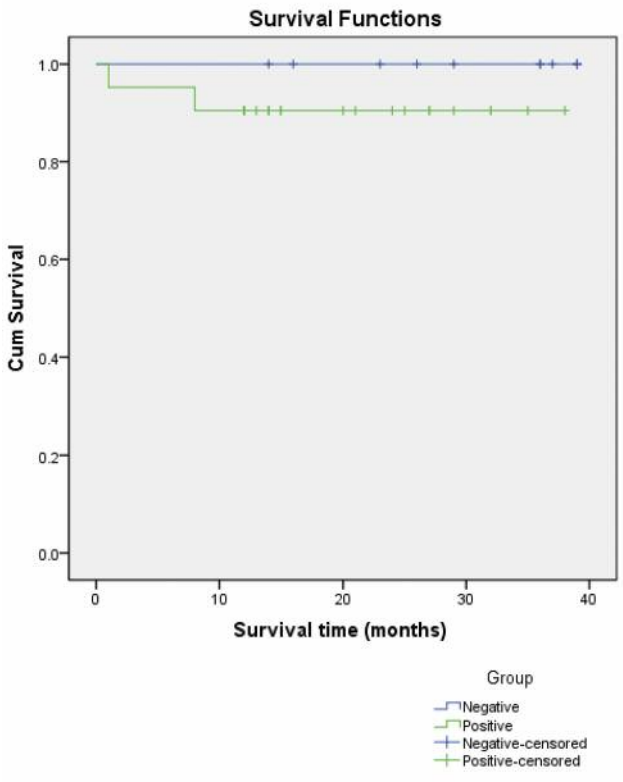

Figure 2. *Analysis of 1-year overall survival (OS). OS rates in patients with Siewert type II/III AEG with or without LNM were 100% and 70%, respectively (p=0.288).*

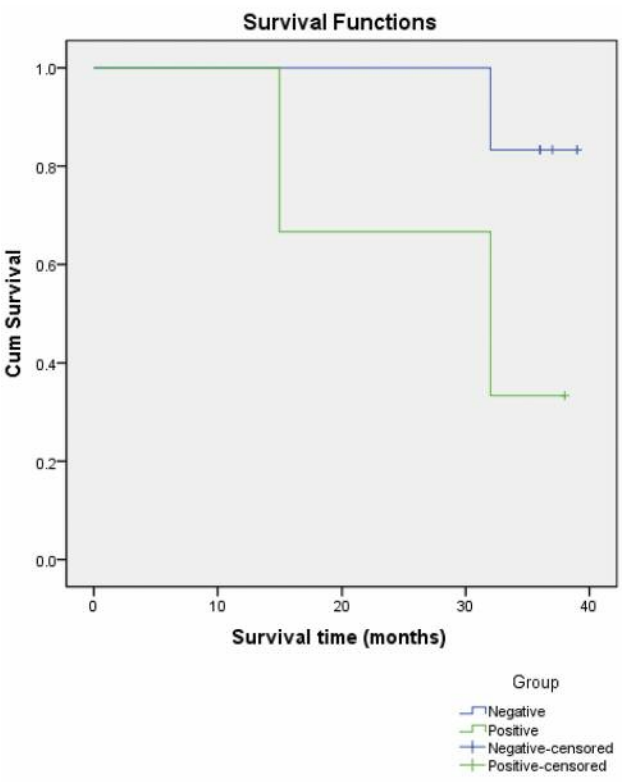

Figure 3. *Analysis of 3-year overall survival (OS). OS rates in patients with Siewert type II/III AEG with or without LNM were 100% and 60%, respectively (p=0.167).*

(p=0.027). Twenty-four patients were found with lymphatic invasion of which 20 were found to be combined with LNM (p=0.009). All differences were statistically significant (p<0.05). On the contrary, there were no correlations between LNM and other factors, including age, gender, tumor location, macroscopic type, operation type and carcinoma nodes (p>0.05) (Table I).

Multivariate analysis results. Multivariate analysis revealed that neoplasms by histological type, lymphatic embolus and depth of infiltration were independent risk factors for LNM in Siewert II/III AEG (p<0.05) (Table IV). LNM of T1 was 5.217-times higher than T2-T4 (95% confidence interval (CI)=1.394-22.613). LNM of poorly differentiated carcinomas was 3.8-times greater than well-differentiated carcinomas (95% CI=0.986-14.656). The positive lymphatic embolus was 5.189-times higher than the negative lymphatic embolus (95% CI=1.298-20.745).

Survival analysis. In the 49 AEG patients included in this study, median follow-up time was 31 months (range=8-39). Death was due to postoperative tumor recurrence in 6 patients, while median survival time was 24.1 months (range=1-39). A total of 14 AEG patients were followed up for over three years postoperatively. Furthermore, 31 AEG patients were followed up over one year postoperatively. The overall survival (OS) rates of 1- and 3-year survival were 93.5% (29/31) and 71.4% (10/14) (Figure 1). One- and three-year survival rates of stage I, stage II and stage III were not statistically significant (χ^2=2.679; p=0.444). However, stage I of AEG may have a better prognosis than stage II and stage III of AEG.

One-year survival rates were 100% for patients without LNM and 70% for patients with LNM; however, the difference between these two groups was not statistically significant (p=0.288, Figure 2). A total of 14 AEG patients were followed up for over three years postoperatively. The difference in 3-year survival was 100% in patients without LNM and 60% in those with LNM (p=0.167, Figure 3). Although the difference was not statistically significant between 1- and 3-year survival between LNM and without LNM, patients without LNM may have a better prognosis than with LNM of AEG.

Table I. *Baseline characteristics of 49 patients and univariate analysis of potential risk factors for lymph node metastasis.*

Variables	Number of patients	Lymph node metastasis (n (%))	χ^2	*p*-Value
Age (years)			0.030	0.862
<60	21	14 (66.7%)		
≥60	28	18 (64.3%)		
Gender			0.707	0.400
Male	43	29 (67.4%)		
Female	6	3 (50%)		
Tumor location			0.729	0.120
Siewert II	36	23 (63.9%)		
Siewert III	13	9 (69.2%)		
Tumor size			10.481	0.001
<2 cm	5	0 (0%)		
≥2 cm	44	32 (72.7%)		
Macroscopic type			3.319	0.190
Elevated	5	3 (60%)		
Flat	4	1 (25%)		
Depressed	40	28 (70%)		
Operative type			0.023	0.879
Proximal gastrectomy	18	12 (66.7%)		
Total gastrectomy	31	20 (64.5%)		
Depth of invasion			28.016	0.000
T1	4	0 (0%)		
T2	5	0 (0%)		
T3	22	15 (68.2%)		
T4	18	17 (94.4%)		
Histologic type			4.864	0.027
Differentiated	24	12 (50%)		
Undifferentiated	25	20 (80%)		
Lymphatic invasion			6.747	0.009
Negative	25	12 (48%)		
Positive	24	20 (83.3%)		
Carcinoma nodes			0.542	0.461
Negative	48	31 (64.6%)		
Positive	1	1 (100%)		

OS, Overall survival.

Table II. *Condition and number of lymph nodes involved (%, n/N).*

Group of lymph nodes	Lymph node metastatic rate (%, n/N)
No.1	48.6 (18/37)
No.2	42.7 (11/26)
No.3	31.6 (12/38)
No.4	9.38 (3/32)
No.5	3.22 (1/31)
No.6	7.41 (2/27)
No.7	22.6 (7/31)
No.8	8.1 (3/37)
No.9	11.1 (3/27)
No.10	0 (0/11)
No.11	17.9 (5/28)
No.12	0 (0/26)
No.19	0 (0/4)
No.20	0 (0/9)

Table III. *Rate of mediastinum lymph node metastases (%).*

Group of lymph nodes			Siewert II (%, n/N)	Siewert III (%, n/N)
No.110			8.3 (3/36)	0 (0/13)
No.111			0 (0/36)	0 (0/13)
No.112	0 (0/36)	0 (0/13)		

Discussion

We retrospectively examined the clinicopathological characteristics, prognostic and risk factors associated with Siewert II/III AEG. With the development of enhanced recovery after surgery (ERAS), it is important to find a precise model of LNM evaluation in order to choose the optimal extent of dissection and establish a reasonable therapeutic schedule.

In order to determine the risk factors of LNM in Siewert II/III AEG, we retrospectively reviewed the clinical data of 49 patients. Several prognostic factors, including depth of infiltration, tumor size, neoplasms by histologic type and lymphatic embolus, have been demonstrated to be related to LNM in AEG. Nomura *et al*. revealed that the rate of LNM in mucosal carcinomas was lower than in submucosal carcinomas (1-6% *vs*. 14-25%), while LNM of submucosal carcinomas was 5.805 times higher than mucosal carcinomas (11). However, it is not only limited to the early gastric cancer. In our study, the observed rate of LNM of Siewert II/III AEG was 0% (0/4) and 71.1% (32/45) in early gastric (T1) and advanced gastric cancer (T2-T4), respectively. It was similar to the results of Duan *et al*. where the incidence of LNM in T2-T4 was slightly higher than in previous studies (12). Due to the lack of standardization in pathological biopsy procedures in our center during the early period, the occurrence of bias in tumor stage is possible. Yasuda *et al*. reported on early gastric cancer that none of their 118 patients had LNM when the depth of infiltration was ≤0.3 mm (13). Furthermore, the frequency of lymph node metastasis for tumors with 0.3 to 1 mm and >1 mm of submucosal invasion was 19% and 14%, respectively. The reason behind this observation may be due to the presence of substantial lymphatic capillaries in the gastric submucosa and the large gap between adjacent endothelial cells. If the tumor infiltrated into the submucosa or deeper, cancer cells

Table IV. *Multivariate analysis of risk factors for lymph node metastases.*

Variables	B	S.E.	Walds	*p*-Value	Exp (B)	Exp (B) 95% CI
Histologic type	1.135	0.689	3.759	0.050	3.800	0.986-14.656
Lymphatic invasion	1.647	0.707	5.423	0.020	5.189	1.298-20.745
Depth of invasion	1.829	0.713	5.545	0.019	5.217	1.394-22.613
Constant	–3.652	1.456	6.290	0.012	0.026	–

B, Partial regression coefficient; S.E., standard error; Exp (B), odds ratio (OR); CI, confidence interval.

could invade the lymphatic capillaries through the endothelial cell space, resulting in LNM.

In terms of histological type and lymphatic invasion, tumor differentiation determines its biological characteristics. Lower degrees of differentiation have higher incidences of LNM. The cause of LNM is that poorly differentiated tumors have higher heterogeneity, resulting in stronger and more aggressive biological characteristics compared to other histological types. In addition, 24 cases were found with a lymphatic embolus of which 20 combined with LNM. The reason may be that endothelial cells consist of a capillary lymphatic wall without a basement membrane and pericyte and an imbricated arrangement. Consequently, lymphatic capillaries have higher permeability than blood capillaries, making them more prone to LNM. Ti *et al*. found a lymphatic invasion in 54 patients; in 51 patients, invasion was combined with LNM increasing, thus, the rate of LNM to 94.4% (14). However, it is difficult to determine the presence of LNM prior to surgery. Thus, tumor size, histologic type and depth of invasion provide a relatively valuable reference

In addition, some related studies have also reported tumor diameter as a risk factor (15). Gotoda *et al*. reported that LNM with a tumor diameter of <1 cm is seldom detected with a rate of 2.8%, while the LNM rate for tumor sizes that range from 1.1 to 2 cm or more, compared to 2 cm, increased to 7.0% and 19.4%. In our analysis, tumor size is an independent risk factor for LNM (16). However, the number of patients included in our study was too small for an in-depth analysis. Therefore, more high-quality studies with a larger sample size are needed in order to draw more definite conclusions.

Long-term survival after curative resection for AEG ranges between 18% and 50% (17). LNM has been confirmed to be one of the most important prognostic factors for gastric cancer (18). Similar to the data in this study, 3-year survival rates of patients without LNM were significantly higher than in patients with LNM, with rates being 100% and 70%, respectively. Although the 3-year survival rates of patients without LNM and with LNM were not statistically significant, postoperative survival of patients without metastatic nodes revealed a longer mean survival time compared to patients with metastatic nodes. Sisic *et al*. found median survival time was not associated with the number of nodes harvested but significantly related to pN stage among all Siewert type II/III AEGs (19). However, Matsuda *et al*. found that the number of lymph node metastases and number of transfer stations have a significant influence on prognosis of Siewert II/III AEG patients (7). With the number of lymph node metastases and transfer stations increasing, the 5-year survival rate is lower. Meanwhile, some studies have reported different patterns of LN metastasis and prognosis in patients with AEG. In 1996, Steup *et al*. demonstrated that for patients with LNs without metastasis, the 5- and 10-year survivals were 72% and 72%, compared with 18% and 16% for patients with diseased nodes, respectively ($p<0.005$) (20). Gu *et al*. examined the number of LNs with metastasis versus long-term survival and demonstrated that the 5- year OS in patients who had one positive LN was similar to the rate in patients in the ypN0 group ($p=0.84$), significantly better, however, than the rate in patients who had more than two positive LNs ($p=0.001$) (21).

For patients with Siewert II/III AEG, the choice of an appropriate surgical approach relies on the accurate assessment of the depth of invasion, histological type and condition of LNMs prior to surgery. The identification of LNM can be achieved via CT or endoscopic ultrasonography. If necessary, a biopsy determines the depth of infiltration and, consequently, a reasonable surgical method. In patients with high-risk factors, radical total gastrectomy combined with standard D2 lymphadenectomy and No.110 lymphadenectomy is recommended.

In conclusion, our study suggests that depth of infiltration, tumor histological type and lymphatic embolus are independent risk factors for LNM in Siewert II/III AEG patients. The survival rate with negative lymph nodes is better than in patients with LNM. Therefore, we hold the opinion that radical total gastrectomy combined with standard D2 lymphadenectomy and No.110 lymphadenectomy is the correct method of treatment. All patients should be regularly followed up after the operation for possible tumor recurrence. Due to the fact that the sample of patients included in this study was relatively small, more high-quality studies or randomized controlled trials are expected in order to further investigate the risk factors and prognosis of Siewert II/III AEG.

Conflicts of Interest

The Authors declare no conflict of interest with this work.

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