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ORIGINAL ARTICLE

Should Pyloric Lymph Nodes Be Dissected for Siewert Type II and III Adenocarcinoma of the Esophagogastric Junctions: Experience from a High-Volume Center in China

Huihua Cao[1] · Marie Ooi[2] · Zhan Yu[1] · Qing Wang[1] · Zhong Li[1] · Qicheng Lu[1] · Yugang Wu[1]

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Abstract

Background The optimal extent of lymph node (LN) dissection remains controversial in adenocarcinoma of the esophagogastric junction (AEG), especially in Siewert types II and III. The aim of this study was to analyze clinicopathological characteristics of patients with Siewert type II and III AEGs to clarify whether pyloric (no. 5 and no.6) lymphadenectomy is essential in these patients.

Methods A retrospective analysis was performed in the Third Affiliated Hospital of Soochow University from September 2008 to December 2012, and clinicopathological characteristics on all patients with Siewert type II and III AEGs, who underwent curative total gastrectomy with lymphadenectomy were collected. The index of estimated benefit from lymph node dissection (IEBLD) was used to evaluate the efficacy of lymph node dissection of no. 5 and no. 6. Both clinicopathological characteristics and IEBLDs were set as the standards in the assessment of the value of pyloric lymph nodes dissection.

Results A total of 216 patients with AEG (Siewert type II: 141, Siewert type III: 75) were included into the study. Type III AEG had a larger tumor size and relatively advanced T stage compared to Type II AEG. The 5-year overall survival (OS) rates in type II and type III AEGs were almost similar (type II 50.4% vs. type III 46.7%, $p = 0.782$). There was a very low incidence of pyloric lymph nodes metastases in type II AEG (no. 5 is 1.4% and no. 6 is 0.7%). Hence, the IEBLDs of no. 5 and no. 6 lymph node were negligible regardless of the T stage and tumor differentiation. In type III AEG, metastasis rates of no. 5 and no. 6 lymph node were 9.3 and 5.3%, respectively. The IEBLDs of no. 5 and no. 6 lymph node were 2.7 and 1.3, respectively.

Conclusions Based on the IEBLDs of pyloric lymph nodes, dissection of no. 5 and no. 6 lymph nodes were worthwhile for Siewert type III AEG but not essential for Siewert type II AEG.

Keywords Adenocarcinoma of the esophagogastric junction · Lymphadenectomy · Siewert type II · Siewert type III

Introduction

Recently, the incidence of adenocarcinoma of the esophagogastric junction (AEG) which carries a poor prognosis has been rapidly increasing in both Western and Eastern countries.[1–3] AEG is considered as a separate entity compared to gastric adenocarcinoma given the unique location, tumor origin, bio-behavior and clinical outcome. Therefore, treatment strategy for such tumor is different compared to conventional gastric adenocarcinoma. Siewert et al.[4] proposed a classification for AEG and discussed the treatment for each type of AEG. Compared to Siewert type I AEG, Siewert type II and III AEGs take the majority (99% of AEGs) and are more prevalent in Eastern countries.[5]

Resection of primary tumor with regional lymphadenectomy is the traditional surgery for AEG.[3] However, there is currently no consensus on the type of surgical resection and extent of lymphadenectomy for AEGs. According to a national wide survey conducted in Japan,[5] the results showed that Japanese surgeons preferred to omit distal part lymph nodes (LNs) dissection for Siewert type II and III AEGs, whereas in most centers in China, a total gastrectomy and D2

Huihua Cao and Marie Ooi contributed equally to this work.

✉ Qicheng Lu
czyyluqicheng123@163.com

✉ Yugang Wu
czyywyg89@163.com

[1] Department of General Surgery, The Third Affiliated Hospital of Soochow University and The First People's Hospital of Changzhou, Changzhou 213000, Jiangsu, China

[2] Gastroenterology Department, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia

Table 1 Characteristics of AEG II and III ($n = 216$)

Parameters	Siewert type II ($n = 141$)	Siewert type III ($n = 75$)	p value
Age			0.663
Median (range), years	62 (33–81)	60 (39–80)	
Sex			0.610
Male	108 (76.6%)	60 (80%)	
Female	33 (23.4%)	15 (20%)	
Tumor diameter			0.022
Median (range), cm	4.2 (0.2–16.5)	6.5 (0.2–19.5)	
Tumor grade			0.563
G1–2	61 (43.3%)	29 (38.7%)	
G3–4	80 (56.7%)	46 (61.3%)	
LNR			< 0.001
≤ 0.18	67 (47.5%)	64 (85.3%)	
> 0.18	74 (52.5%)	11 (14.7%)	
Pyloric LN metastases			< 0.001
Presence	3 (2.1%)	11 (14.7%)	
Absence	138 (97.9%)	64 (85.3%)	
pT-stage			0.044
T1	29 (20.6%)	9 (12%)	
T2	39 (27.7%)	21 (28%)	
T3	58 (41.1%)	27 (36%)	
T4	15 (10.6%)	18 (24%)	
pN-stage			0.675
N0	42 (29.8%)	21 (28%)	
N1	44 (31.2%)	19 (25.3%)	
N2	28 (19.9%)	15 (20%)	
N3a	16 (11.3%)	10 (13.3%)	
N3b	11 (7.8%)	10 (13.3%)	
TNM stage			0.038
I	41 (29.1%)	11 (14.7%)	
II	53 (37.6%)	29 (38.7%)	
III	47 (33.3%)	35 (46.7%)	

lymphadenectomy is the routine strategy for gastric cancer. Considering the high incidence of complications[6] and nutrition disorders[7] after total gastrectomy, proximal gastrectomy may be a better choice for the Siewert type II and III AEGs if a negative margin can be achieved. The aim of the study was to investigate the value of distal lymph nodes (no. 5 and no. 6 lymph nodes), also known as pyloric lymph node dissection in both Siewert type II and III AEGs.

Methods

Patients

From September 2008 to December 2012, all medical records of patients with Siewert type II and III AEGs at The Third Affiliated Hospital of Soochow University were reviewed retrospectively. The inclusion criteria were as follows: (1) histological confirmed adenocarcinoma with an epicenter within 1 cm above and 2 cm below esophagogastric junction (EGJ) defined as Siewert type II or within 2 to 5 cm below EGJ as Siewert type III, (2) did not receive neoadjuvant chemoradiation, (3) underwent a transabdominal R0 total gastrectomy and D2 lymphadenectomy, (4) with no evidence of distant metastasis. Follow-up was conducted by either a mail, a telephone call, or a clinic consultation. Informed consent was obtained from all patients, and this study was approved by the ethics committee of The Third Affiliated Hospital of Soochow University.

Index of Evaluation

The index of estimated benefit from lymph node dissection (IEBLD) proposed by Sasako M et al.[8] was used in this study to evaluate the efficacy of lymph node dissection of no. 5 and no. 6 stations. The index is calculated by multiplying the metastatic rate of a certain lymph node station by the 5-year survival rate of corresponding metastatic patients. IEBLD = 0 is defined as no value in lymph node dissection of no. 5 and no. 6 stations. IEBLD > 0 is defined as having a therapeutic value for lymph node dissection and the higher the index the more beneficial for lymphadenectomy.

Pathological characteristics were also taken into account. We divided the patients into two groups based on lymph node ratio (LNR), tumor depth (T), and tumor grade (G). LNR is defined as the ratio of positive LNs-to-the total number of retrieved LNs. We chose the median LNR as a cut-off point to divide the gastric cancer patients. Group T1–2 included T1 (lamina propria, muscularis mucosa, and submucosa invasion) and T2 (muscularis propria invasion). Group T3–4 included T3 (subserosa invasion) and T4 (serosa and adjacent organ invasion).[9] Group G1–2 included G1 defined as a well differentiated tumor and G2 defined as a moderately differentiated tumor. Group G3–4 included G3 defined as poorly differentiated and G4 defined as undifferentiated.

Statistics

All statistical analyses were performed using SPSS 17.0. Chi-square test was used to compare categorical variables. Kaplan-Meier analysis was used to determine the survival and log-rank test was used to compare the patient survival between subgroups. Univariate and multivariate analyses were performed using a Cox proportional hazards model. All statistical analysis was two-sided and $P < 0.05$ was regarded as statistically significant.

Table 2 Univariate and multivariate analysis of prognostic factors

Parameters	No.	5-year OS Rate (%)	Univariate analysis *P*	Multivariate analysis		
				HR	95% CI	*P*
Age			0.423			
≤ 65	139	52.5				
> 65	77	45.5				
Sex			0.446			
Male	168	47.6				
Female	48	58.3				
Siewert type			0.782			
II	141	50.4				
III	75	46.7				
Tumor diameter			0.872			
≤ 6 cm	109	50.5				
> 6 cm	107	49.5				
pT-stage			< 0.001	2.014	1.252–3.336	0.011
T1–2	98	63.3				
T3–4	118	37.3				
Tumor differentiation			0.007	1.744	0.962–2.688	0.266
G1–2	90	58.9				
G3–4	126	42.1				
Pyloric LN metastases			0.029	1.512	1.018–2.221	0.023
Presence	14	21.4				
Absence	202	51.0				
LNR			< 0.001	3.224	1.899–6.326	0.001
≤ 0.18	131	64.1				
> 0.18	85	25.9				

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *LN* lymph nodes, *LNR* lymph node ratio

Results

Patient Characteristics

A total of 216 patients were included for analysis. The clinicopathological characteristics of these patients are listed in Table 1. There were 141 patients with Siewert type II AEG and 75 patients with Siewert type III AEG. The median age in the patients with Siewert type II and Siewert type III AEGs were 62 years (range, 33–81 years) and 60 years (range, 39–80 years), respectively.

The percentage of T3–4 patients in Type III AEG and Type II AEG were 60% versus 51.7%, respectively. Hence, more advanced tumors were detected in type III AEG ($P = 0.044$). Histologically, 90 patients were in G1–2 and 126 patients were in G3–4 with no difference found between the two types of AEGs ($P = 0.563$).

Survival Analysis

In this study, all patients were followed up for more than 5 years. The 5-year overall survival (OS) rate was 50%. The median LNR was 0.18, thus we classified the patients into two subgroups. Univariate analysis demonstrated tumor differentiation, pT-stage, pyloric LN metastases, and LNR were significant prognostic factors for AEG. However, based on multivariate analysis, tumor differentiation was not statistically significant as a prognostic factor (Table 2). Figure 1 shows the survival curves of all patients classified by LNR. The 5-year OS rates in group LNR ≤ 0.18 and group LNR > 0.18 were significantly different (LNR ≤ 0.18 64.1% vs. LNR > 0.18 25.9%, $P < 0.001$). Figure 2 shows the survival curves of all patients classified by the Siewert type. The 5-year OS rates in type II and III AEGs were almost similar (type II 50.4% vs. type III 46.7%, $P = 0.782$). The Siewert type III

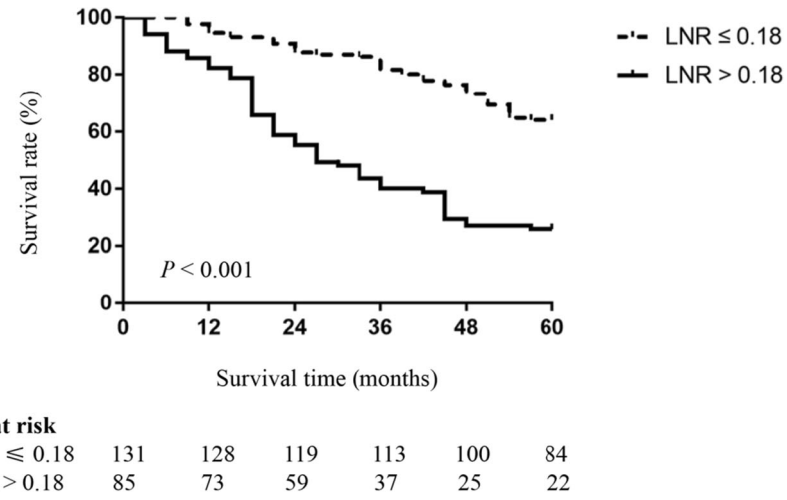

Fig. 1 Overall survival in patients by LNR

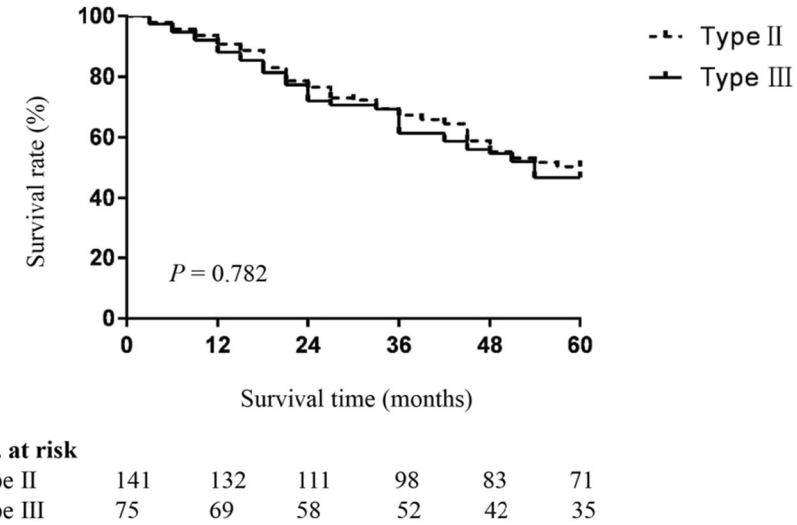

Fig. 2 Overall survival in patients by Siewert type

AEG appears to have a worse prognosis than Siewert type II AEG, but was not statistically significant. Figure 3 shows the survival curves of all patients classified by tumor depth (Fig. 3a) and tumor grade (Fig. 3b). The 5-year OS rates in group T1–2 and group T3–4 were significantly different (T1–2 63.3% vs. T3–4 37.3%, $P < 0.001$). The 5-year OS rates in group G1–2 and group G3–4 were significantly different (G1–2 58.9% vs. G3–4 42.1%, $P = 0.007$). Figure 4 shows the survival curves of all patients classified by Siewert type with tumor depth (Fig. 4a) and Siewert type with tumor grade (Fig. 4b). The 5-year OS rates in the 4 groups in Fig. 4a were significantly different (AEG II T1–2 64.7% vs. AEG II T3–4 42.5% vs. AEG III T1–2 60.0% vs. AEG III T3–4 28.9%, $P < 0.001$). Similarly, the 5-year OS rates in the 4 groups in Fig. 4b were significantly different (AEG II G1–2 63.9% vs. AEG II G3–4 45.0% vs. AEG III G1–2 48.3% vs. AEG III G3–4 37.0%, $P = 0.035$). Figure 5 shows the survival curves of all patients classified by whether having pyloric lymph nodes metastases. The 5-year OS rates in the 2 groups were significantly different (non-pyloric LN metastases 51.0% vs. pyloric LN metastases 21.4%, $P = 0.029$).

Estimated Benefit from Pyloric Lymph Node Dissection

Table 3 shows the IEBLDs for no. 5 and no. 6 lymph nodes, based on tumor depth and tumor grade for Siewert type II AEG. Index listed in Table 4 is for Siewert type III AEG. Out of 141 Siewert type II AEG, only 2 patients had no. 5 lymph node metastasis and the incidence of no. 5 lymph node metastasis was 1.4%, only 1 patient had no. 6 lymph node metastasis and the incidence of no. 6 lymph node metastasis was 0.7%. None of the AEG II patients with the lymph nodes involved lived longer than 5 years. Hence, the IEBLDs of no. 5 and no. 6 lymph node stations were all zero regardless of tumor depth or tumor grade. However, in 75 Siewert type III AEG, seven patients had no. 5 lymph node metastasis and the incidence of no. 5 lymph node metastasis was 9.3%, multiplying with the 5-year survival rate, the IEBLD of no. 5 lymph nodes was 2.7. Four patients had no. 6 lymph node metastasis and the incidence of no. 6 lymph node metastasis was 5.3%, multiplying with the 5-year survival rate, the IEBLD of no. 6 lymph nodes was 1.3.

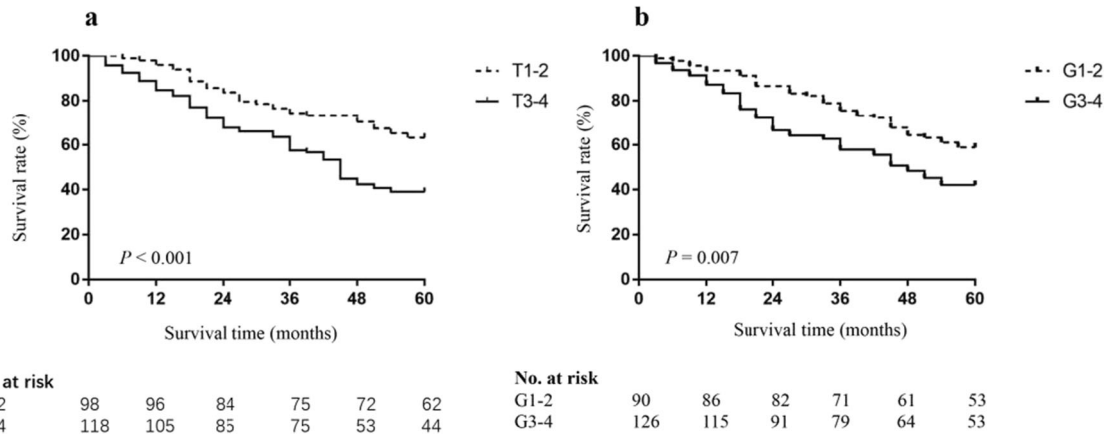

Fig. 3 Overall survival in patients by tumor depth **a** and tumor grade **b**

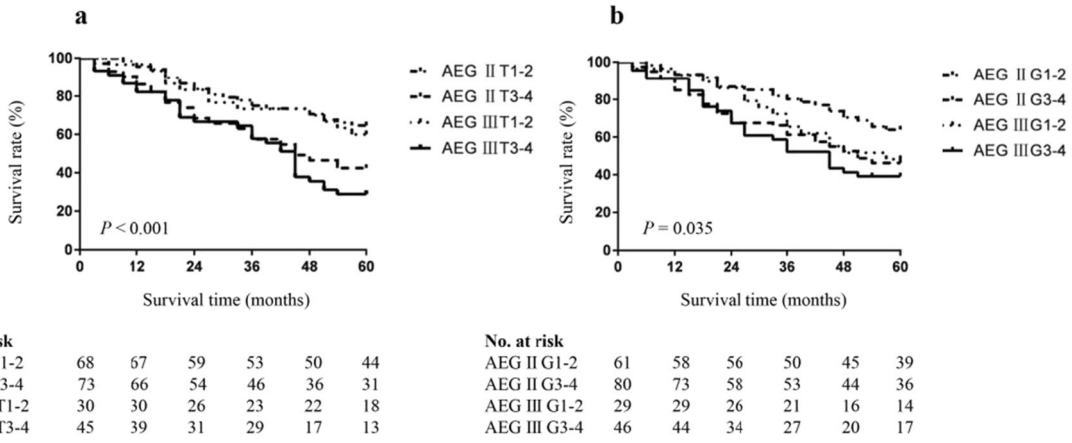

Fig. 4 Overall survival in patients by Siewert type with tumor depth **a** and Siewert type with tumor grade **b**

This different IEBLD distribution may indicate the value of no. 5 and no. 6 lymph node dissections in AEG III, especially for the advanced ones.

Discussion

In Asian countries, the prevalence of adenocarcinoma of the esophagogastric junction (AEG) is lower than that of gastric cancer. Majority of AEGs are Siewert type II and III AEGs. The incidence and clinicopathological characteristics of AEG in the East are different compared to the West.[10] Previously, AEG was staged as esophageal cancer in the seventh edition of the International Union Against Cancer (AJCC/UICC) staging system.[11] However, the eighth edition of TNM staging system was established and AEGs may be attributed to gastric cancers or esophageal cancers according the location of tumor epicenter to EGJ.

A total gastrectomy is conventional curative treatment option for Siewert type II and III AEGs. In this study, all patients underwent a transabdominal total gastrectomy with Roux-en-Y reconstruction by the major blood supply from the jejunum and esophagus. For Siewert type II AEG, the esophagus was accessed at least 3–5 cm above the esophagogastric junction to guarantee proximal margin negative. However, malnutrition was inevitable after total gastrectomy.[6] As Bae JM et al.[7] reported, inadequate oral intake and fat malabsorption from total gastrectomy and reconstruction of the digestive tract contributed to malnutrition.

In addition, esophagojejunal anastomosis leakage is a major complication that can be life-threatening.[12] The rate of esophagojejunal anastomosis leakage ranges from 1 to 20% with a high mortality rate that ranges from 25 to 50%.[13]

Compared to a total gastrectomy, proximal gastrectomy has the advantages of being less invasive, less challenging surgical techniques, and less risk of malnutrition.[14] However, the disadvantages of proximal gastrectomy include higher risk of reflux esophagitis, dysphagia, and anastomotic stenosis.[15–17]

The reason proximal gastrectomy is not widely accepted as the standard surgical resection for esophagogastric adenocarcinoma is due to the associated complications and oncological outcome. If proximal gastrectomy was performed, an esophagogastrostomy anastomosis would be the simplest and most commonly used reconstruction method. A jejunal interposition or double-tract reconstruction can be alternatively adopted to prevent gastroesophageal reflux.[18]

In the current study, pT-stage, pyloric LN metastases, and LNR were independent prognostic factors for OS. Aratani K

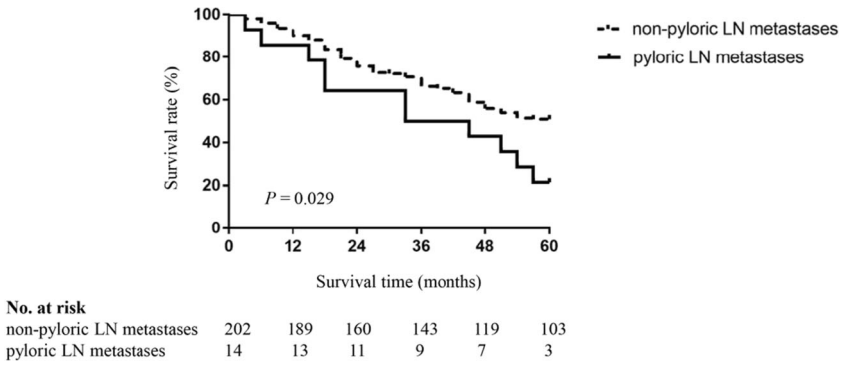

Fig. 5 Overall survival in patients by whether having pyloric lymph nodes metastases

Table 3 IEBLDs of no. 5 and 6 lymph nodes in patients with AEG II by tumor depth and tumor grade

Lymph node station	Tumor depth/ tumor grade	Number of patients with metastasis	Number of patients with dissection	Incidence of lymph node metastasis (%)	5-year survival rate of patients with metastasis (%)	IEBLD
5	All	2	141	1.4	0	0
	T1–2	0	68	0	0	0
	T3–4	2	73	2.7	0	0
	G1–2	0	61	0	0	0
	G3–4	2	80	2.5	0	0
6	All	1	141	0.7	0	0
	T1–2	0	68	0	0	0
	T3–4	1	73	1.4	0	0
	G1–2	0	61	0	0	0
	G3–4	1	80	1.25	0	0

IEBLD index of estimated benefit from lymph node dissection

Note: Among 68 patients with T1–T2 stage who accepted pyloric (no. 5 and no. 6) lymph node dissection, there is no one having pyloric lymph node metastases. The usage range of 5-year survival rate is among those having metastases. So, the 5-year survival rate of patients with metastases was zero. G1 and G2 patients are of the same condition

et al.[19] concluded pT-stage and pN-stage were associated with OS and a more advanced tumor stage was associated with poorer OS. Similar conclusions were also drawn by Hosoda K et al., who concluded that lymphatic invasion and lymph node ratio affected OS.[20]

IEBLD an index of estimated benefit from lymph node dissection proposed in 1995 was used to estimate the therapeutic value of lymph node dissection that circumvented the phenomenon of stage migration regardless of nodal metastasis to any other station.[8] Despite its advantages of eliminating stage migration and preventing "unfair selection," there is still no consensus in the threshold of benefit. Based on retrospective data, the IEBLD of each lymph node station in D2 range was at least 1.6;[8] so, we used this data as a reference. The IEBLD we used in this study was based on the assumption of that patients who survived 5 years after resection of lymph nodes metastases would not have done so if the involved lymph nodes that had been left in situ are justified by the dismal survival of those in whom unresected involved nodes are seen and recorded at operation. In this study, we analyzed 216 patients with Siewert type II and III AEGs using IEBLDs of pyloric lymph node stations to provide fundamental evidence to support the optimal choice of surgical approaches for Siewert type II and III AEGs.

In our results, the AEG II and III had an almost similar survival curves postoperatively which was consistent with Goto H et al. study,[1] who analyzed 92 patients with Siewert type II AEG and 40 patients with Siewert type III AEG. They found the IEBLDs of no. 5 and no. 6 lymph node stations were both zero in Siewert type II AEG, while in Siewert type III AEG, the IEBLD of no. 5 lymph node station and no. 6 lymph node station were 2.6 and 0, respectively. Similarly, Hosoda K et al. study[20] also demonstrated the IEBLDs of no. 5 and no. 6 lymph node station were both zero in Siewert type II AEG.

Table 4 IEBLDs of no. 5 and 6 lymph nodes in patients with AEG III by tumor depth and tumor grade

Lymph node station	Tumor depth/ Tumor grade	Number of patients with metastasis	Number of patients with dissection	Incidence of lymph node metastasis (%)	5-year survival rate of patients with metastasis (%)	IEBLD
5	All	7	75	9.3	28.6	2.7
	T1–2	2	30	6.7	50	3.4
	T3–4	5	45	11.1	20	2.2
	G1–2	3	29	10.3	33.3	3.4
	G3–4	4	46	8.7	25	2.2
6	All	4	75	5.3	25	1.3
	T1–2	1	30	3.3	0	0
	T3–4	3	45	6.7	33.3	2.2
	G1–2	2	29	6.9	0	0
	G3–4	2	46	4.3	50	2.2

IEBLD index of estimated benefit from lymph node dissection

However, both of these studies did not investigate IEBLDs based on tumor depth and tumor grade. According to our results, for Siewert type II AEG, IEBLDs of no. 5 and no. 6 lymph node station were both zero regardless of the tumor depth and tumor grade. Based on the IEBLDs of no. 5 and no. 6 lymph node, we draw a conclusion that for Siewert type II AEG the dissection of the pyloric lymph nodes may not be necessary and the distal stomach could be preserved.[10, 21, 22]

For Siewert type III AEG, the IEBLDs of no. 5 and no. 6 lymph node stations were all higher than two, which had therapeutic value for lymphadenectomy, except for no. 6 lymph node station in T1–2 and G1–2 groups where both IEBLDs were zero. The IEBLDs of Siewert type III AEG were higher than those of Siewert type II AEG. Miwa K et al.[23] reported that lymphatic flow to the lower perigastric lymph nodes was from the middle third of the stomach. Siewert type III AEG were typically large enough to invade the middle third of the stomach, which accounts for the involvement of no. 5 and no. 6 lymph node stations in Siewert type III AEG. Our results supported the adoption of a total gastrectomy with lymphadenectomy in Siewert type III AEG.[24]

This study has some limitations. The retrospective study designed from a single center and the relative small sample size may result in selection bias. We only use overall survival in this study. To enhance the study rigor and persuasiveness, it is better to include the disease specific survival (DSS) because D2 lymphadenectomy also has survival benefit in terms of DSS.[25] Besides, a comparison between total and proximal gastrectomies in Siewert type II and III AEGs may be more straightforward, so a further prospective study is warranted to confirm our results.

In summary, we proposed that a total gastrectomy with lymphadenectomy should be selected for Siewert type III AEG. However, Siewert type II AEG may only need a proximal partial gastrectomy with preservation of the distal stomach and pyloric lymph nodes dissection may not be necessary. In order to prevent, a gastroesophageal reflux, jejunal interposition or double-tract reconstruction can be adopted. However, a larger prospective study is obviously required to validate these findings.

Author Contribution Huihua Cao and Marie Ooi wrote the manuscript and analyzed clinicopathological data. Zhan Yu, Qing Wang and Zhong Li carried out the follow-ups and collected the clinicopathological data of patients. Yugang Wu and Qicheng Lu assisted Huihua Cao and Marie Ooi to complete the work and Yugang Wu funded the study.

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Compliance with Ethical Standards

Disclosures The authors have no financial conflict of interest.

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