

# Priority of lymph node dissection for advanced esophagogastric junction adenocarcinoma with the tumor center located below the esophagogastric junction

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## Abstract

To clarify the priority of lymph node dissection (LND) in advanced Siewert type II and III AEG, in which the center of the tumor is located below the esophagogastric junction (EGJ).

Data in 395 patients with advanced Siewert type II or III AEG was analyzed retrospectively. The index of estimated benefit from LND (IEBLD) was used to evaluate the efficacy of LND for each nodal station.

The mean number of dissected LNs did not differ significantly between patients with type II and III AEG, nor did the mean number of retrieved LNs at each station significantly differ between the 2 groups. According to the IEBLD, the dissection of parahiatal LNs (No.19 and 20) and LNs along the distal portion of the stomach (No.5, 6, and 12a) seemed unlikely to be beneficial, whereas the dissection of Nos.1–3, 7, 9 and 11p yielded high therapeutic benefit (IEBLD>3.0) in both groups. The IEBLDs of No.4d, 8a, and 10 were much higher in type III than in type II AEG cases. No.10 LND may improve survival for type III AEG cases (IEBLD = 2.9), especially for subgroups with primary tumors invading the serosa layer, undifferentiated cancers, macroscopic type 3–4 tumors and tumors  $\geq 50$  mm in size (all IEBLDs > 4.0).

For advanced AEG located below the EGJ, the dissection of paracardial LNs, lesser curvature LNs, and LNs around the celiac axis would promote higher survival benefits regardless of the Siewert subtype. Patients with type III AEG, especially those with serosa-invasive tumors, undifferentiated tumors, macroscopic type 3–4 tumors and tumors  $\geq 50$  mm in size may obtain relatively higher survival benefits from No. 10 lymphadenectomy.

**Abbreviations:** AEG = adenocarcinoma of the esophagogastric junction, BMI = body mass index, EGJ = esophagogastric junction, IEBLD = index of estimated benefit from lymph node dissection, LND = lymph node dissection, LNM = lymph node metastasis, RTG = radical total gastrectomy.

**Keywords:** esophagogastric junction carcinoma, IEBLD, lymphadenectomy, Siewert classification

The incidence of adenocarcinoma of the esophagogastric junction (AEG) has recently noticeably increased.<sup>[1,2]</sup> AEG is classified into 3 subgroups according to the tumor location relative to the

esophagogastric junction (EGJ) by Siewert: type I, located within 1 and 5 cm above the anatomic EGJ; type II, located within 1 cm above and 2 cm below the EGJ; and type III, located within 2 and 5 cm below the EGJ.<sup>[3]</sup> Siewert type II or III AEG is more frequent in Asian countries, which differs from western reports.<sup>[4]</sup> Abdominal lymph node metastasis (LNM) are present in the majority of Siewert type II and III AEG cases, but there are nonetheless some differences between type II and III AEG with respect to the incidence of LNM because the biological behavior of AEG differs among types.<sup>[5]</sup>

AEG was categorized as an esophageal cancer by the 7th edition of the TNM classification regardless of the Siewert subtypes,<sup>[6]</sup> whereas the 8th edition of the TNM classification clarified that AEG located within 2 cm of the anatomic EGJ should be treated as esophageal cancer; tumors located greater than 2 cm below the EGJ should be staged as gastric cancer.<sup>[7]</sup> Hence, for AEG with an epicenter located below EGJ, Siewert type II AEG should be staged as esophageal cancers, and type III AEG are to be staged as gastric cancers according to the current TNM classification.<sup>[7]</sup>

However, esophageal adenocarcinomas and gastric cancers exhibit different characteristics, and priority of LN dissection (LND) also differs. Recently, some studies have adopted the index of estimated benefit from LND (IEBLD) to assess value of LND for type II and III AEG,<sup>[8,9]</sup> but priority of LND for advanced type

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II/III AEG remains unclear. Most studies have demonstrate that the survival benefits of dissection of paracardial LNs and lesser curvature LNs for AEG.<sup>[4]</sup> However, efficacy of the dissection of LNs around the celiac axis and splenic hilar LNs for AEG whose tumor epicenter is located below EGJ will need to be clarified more fully. Thus, this study was aimed to reveal whether the optimal extend of LND differs between advanced type II and III AEG located below the EGJ by calculating the IEBLD of each nodal station.

## 1. Material and methods

### 1.1. Patients

Between January 2008 and March 2015, 583 patients with primary advanced Siewert type II or III AEG underwent radical total gastrectomy using the transabdominal approach at the General Surgery Division, Zhangzhou Affiliated Hospital of Fujian Medical University. Inclusion criteria were as follows: histologically proven AEG; tumor center located below the EGJ; pathological T2-T4a tumors; and R0 resection. Exclusion criteria: distant metastasis including peritoneal lavage cytology positive results; preoperative radiotherapy or chemotherapy, tumor invasion greater than 3cm into the esophagus, and incomplete pathological or follow-up data. Ultimately, 395 patients were included in this research. Staging was based on the UICC-TNM 7th edition.<sup>[6]</sup> All patients underwent a lymphadenectomy performed by the same group of surgeons based on the Japanese classification of gastric carcinoma.<sup>[10]</sup> LN No. 1–7, 8a, 9, 11p, and 12a were dissected routinely for each patient. For T3 or deeper tumors located at the greater curvature of the stomach, No.10 lymphadenectomy was performed routinely. The necessity of a dissection of parahiatal LNs (No. 19 and 20) was evaluated based on the preoperative examination and intraoperative exploration. Adjuvant 5-fluorouracil-based chemotherapy after surgery was recommended for every patient. This study was approved by the Ethics committee of Zhangzhou Affiliated Hospital of Fujian Medical University. Informed consent was obtained from all patients for their information to be used for research.

### 1.2. IEBLD

We evaluated therapeutic value of LND of each nodal station based on a concept of IEBLD introduced by Sasako et al.<sup>[11]</sup> This index is calculated by multiplication of the rate of LNM to the station and the 5-year survival rate of patients with metastasis to that station. The incidence of LNM and the 5-year survival rate for patients with LNM was calculated for each station independently, without any reference to LNM at other stations.

### 1.3. Follow-up

Patients were followed up every 3 months after surgery and offered a physical examination, chest radiography, laboratory tests, annual endoscopic examination, and computed tomography. Every patient was followed for 5 years, after which time the follow-up ceased. Survival time was calculated from the date of surgery to death or until the final follow-up date. The 5-year survival rate is determined by dividing the number of patients who survived 5 years by the total number of observed patients.

## 1.4. Statistical analysis

All statistical analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL). Normally distributed data were presented as the mean  $\pm$  SD and compared using Student *t* test. Chi-Squared test or Fisher exact test were used to compare proportions for clinicopathological variables.  $P < .05$  values were considered to indicate statistical significance.

## 2. Results

### 2.1. Clinicopathological characteristics of the patients

The clinicopathological features of all 395 patients are showed in Table 1. There were 167 (42.3%) patients with type II AEG and 228 (57.7%) patients with type III AEG. Type III AEG cases exhibited larger tumor sizes (60.8mm vs 47.3mm,  $P < .001$ ), higher rates of undifferentiated tumors (59.2% vs 48.5%,  $P = .035$ ), deeper tumor invasion (92.5% vs 82.5%,  $P = .007$ ), higher rate of macroscopic type 3–4 (58.3% vs 41.7%,  $P = .035$ ), and more extensive LNM (82.0% vs 67.1%,  $P < .001$ ) than type

**Table 1**  
Clinicopathological characteristics of patients.

Characteristics	Total N = 395	Type II N = 167	Type III N = 228	P-value
Age (year)				.325
Mean (Ixx $\pm$ s)	63.1 $\pm$ 10.4	63.2 $\pm$ 9.6	64.5 $\pm$ 11.5	
Gender				.940
Male	321	136	185	
Female	74	31	43	
BMI, kg/m <sup>2</sup>				.763
Mean (Ixx $\pm$ s)	22.1 $\pm$ 2.9	22.0 $\pm$ 2.8	22.1 $\pm$ 3.0	
Comorbidity				.898
Yes	122	51	71	
No	273	116	157	
ASA status				.358
1	221	99	122	
2	116	48	68	
3	58	20	38	
Tumor size (mm)				<.001
Mean (x $\pm$ s)	54.9 $\pm$ 20.4	47.3 $\pm$ 20.1	60.8 $\pm$ 20.0	
Macroscopic type				.002
Type 0–2	167	78	69	
Type 3–4	203	70	133	
Unclassifiable	45	19	26	
Histological type				.035
Differentiated	173	86	93	
Undifferentiated	222	81	135	
pTcategory				.007
T2	46	29	17	
T3	139	59	80	
T4a	210	79	131	
pN category				<.001
N0	96	55	41	
N1	68	32	36	
N2	82	37	45	
N3	149	43	106	
TNM stage				<.001
IB	27	20	7	
II	115	56	59	
III	253	91	162	
Number of dissected LNs	33.1 $\pm$ 13.5	32.6 $\pm$ 15.8	33.5 $\pm$ 11.4	.535
Number of metastatic LNs	6.5 $\pm$ 7.7	4.8 $\pm$ 6.5	7.6 $\pm$ 8.3	<.001

ASA = American Society of Anesthesiologists, BMI = body mass index.

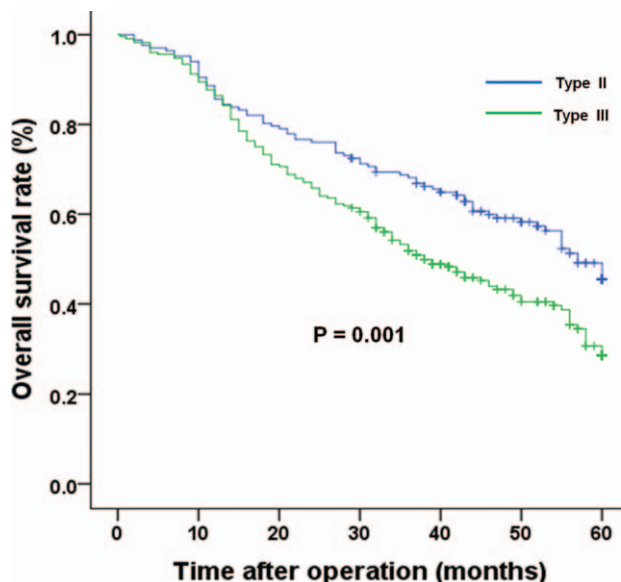


Figure 1. Comparison of overall survival rates between Siewert type II and III AEG.

II AEG cases. There was no significant difference in number of harvested LNs between the 2 groups (33.5 vs 32.6,  $P = .535$ ) (Table 1).

**2.2. Oncologic outcomes**

The type II AEG group showed superior overall survival rate compared to type III tumor group (45.5% vs 28.6%,  $P = .001$ ) (Fig. 1).

**2.3. Comparison of LND and LNM between Siewert type II and III AEG at each station**

The mean number of dissected LNs at each station was compared and did not exhibit any significant differences between type II and III AEG cases (Fig. 2). LNM was more frequent in LN No.1–3, 7, 9, and 11p (exceeding 10.0%) in both 2 groups. The metastatic rates of LN No.4d, 8a, and 10 were much higher in type III AEG group (Table 2).

**2.4. Comparison of IEBLD between Siewert type II and III AEG at each station**

According to the IEBLD, the dissection of parahiatal LNs (No. 19 and 20) and LNs along the distal stomach (No.5, 6 and 12a) seemed not beneficial whereas the dissection of paracardial (No. 1 and 2), lesser curvature (No.3) LNs, and LNs around the celiac axis (No. 7, 9, and 11p) would yield high therapeutic benefit (IEBLD > 3.0) in both groups. The dissection of LN No. 4d, 8a, and 10 had greater therapeutic benefit for type III AEG cases (Table 2).

**2.5. IEBLD of LN No.10 in subgroups with each clinicopathological factor for Siewert type III AEG**

In type III AEG, the IEBLD of LN No.10 was 2.9. The index was greater than 4.0 in patients subgroups with serosa-invasive tumors (5.1), undifferentiated tumors (4.3), macroscopic type 3–4 tumors (4.7) and tumors  $\geq 50$ mm in size (4.1) (Table 3).

**3. Discussion**

Most AEGs are identified as advanced stage disease with poor prognosis, and radical surgery remains the primary treatment.<sup>[12]</sup> Siewert classification of AEG is useful to select the appropriate

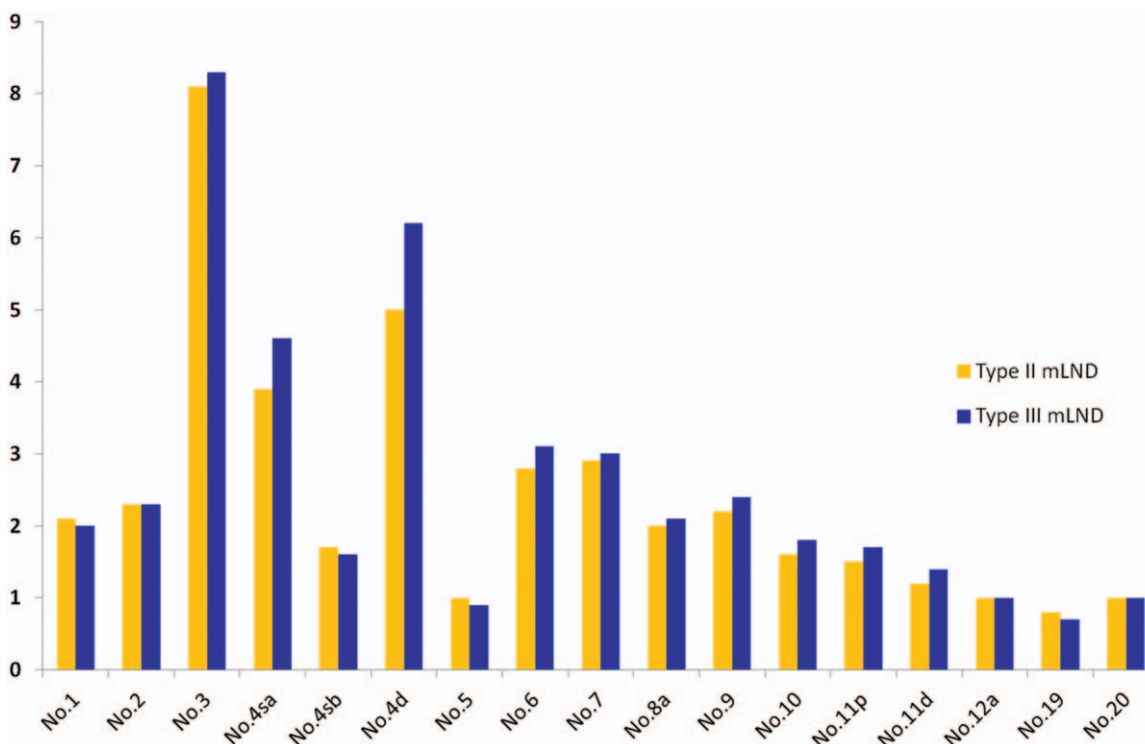


Figure 2. Comparison of LND between Siewert type II and III AEG at each station.

**Table 2****Comparison of metastatic incidence, 5-year survival rate and IEBLD between type II and III AEG at each station.**

Station	No. of LNM		No. of LND		Metastatic incidence (%)		5-year survival rate (%)		IEBLD	
	Type II	Type III	Type II	Type III	Type II	Type III	Type II	Type III	Type II	Type III
No.1	59	102	167	228	35.3	44.7	37.3	33.3	13.2	14.9
No.2	51	80	167	228	30.5	35.1	29.4	28.8	9.0	10.1
No.3	92	153	167	228	55.1	67.1	41.3	25.5	22.8	17.1
No.4sa	3	7	167	228	1.8	3.1	0.0	28.6	0.0	0.9
No.4sb	2	4	167	228	1.2	1.8	50.0	25.0	0.6	0.5
No.4d	5	23	167	228	3.0	10.1	0.0	30.4	0.0	3.1
No.5	1	3	167	228	0.6	1.3	0.0	0.0	0.0	0.0
No.6	0	0	167	228	0.0	0.0	NA	NA	NA	NA
No.7	33	57	167	228	19.8	25.0	39.4	40.4	7.8	10.3
No.8a	11	28	167	228	6.6	12.3	18.2	25.8	1.2	3.2
No.9	19	39	167	228	11.4	17.1	31.6	23.1	3.6	4.0
No.10	2	9	40	68	5.0	13.2	0.0	22.2	0.0	2.9
No.11p	18	35	167	228	10.8	15.3	29.4	22.9	3.2	3.5
No.11d	4	10	167	228	2.4	4.4	0.0	0.0	0.0	0.0
No.12a	2	0	167	228	1.2	0.0	0.0	0.0	0.0	NA
No.19	5	6	58	73	8.6	8.2	0.0	0.0	0.0	0.0
No.20	4	6	65	88	6.2	6.8	25.0	16.7	1.6	1.1

IEBLD = index of estimated benefit from lymph node dissection, LND = lymph node dissection, LNM = lymph node metastasis.

surgical strategy and has been accepted worldwide.<sup>[13]</sup> The biological characteristics of AEG differ among the unique subtypes.<sup>[14,15]</sup> Therefore, the priority of lymphadenectomy for Siewert type II and III AEG remains fairly controversial. The IEBLD represents a reasonable method to assess the efficacy of

LND using by many studies.<sup>[8,9,16,17]</sup> Studies have demonstrated that priority of LND for AEG is different between type II and III tumor groups.<sup>[18,19]</sup> The new edition of the TNM classification proposed that type II AEG with a tumor center below the EGJ should be categorized as an esophageal cancer, whereas type III

**Table 3****IEBLD of No.10 LNs in subgroups with each clinicopathological factor for Siewert type III AEG.**

Clinicopathological factor	No. of LNM	No. of LND	Metastatic incidence (%)	5-year survival rate (%)	IEBLD
Age (year)					
<65	6	39	15.4	16.7	2.6
≥65	3	29	10.3	33.3	3.4
Gender					
Male	8	61	13.1	25.0	3.3
Female	1	7	7.7	0.0	0.0
BMI, kg/m <sup>2</sup>					
<25	5	40	12.5	20.0	2.5
≥25	4	28	14.3	25.0	3.6
Comorbidity					
Yes	3	11	27.3	0.0	0.0
No	6	57	10.5	33.3	3.5
ASA status					
1	3	31	9.7	25.0	3.2
2	3	28	10.7	33.3	3.6
3	3	9	33.3	0.0	0.0
Tumor size (mm)					
<50	0	19	0.0	0.0	0.0
≥50	9	49	18.4	22.2	4.1
Macroscopic type					
Type 0–2	2	15	6.7	0.0	0.0
Type 3–4	6	43	14.0	33.3	4.7
Unclassifiable	1	10	10.0	0.0	0.0
Histological type					
Differentiated	2	21	9.5	0.0	0.0
Undifferentiated	7	47	14.9	28.6	4.3
pTcategory					
T2	0	7	0.0	0.0	0.0
T3	1	22	4.5	0.0	0.0
T4a	8	39	20.5	25.0	5.1

ASA = American Society of Anesthesiologists, BMI = body mass index, IEBLD = index of estimated benefit from lymph node dissection, LND = lymph node dissection, LNM = lymph node metastasis.

AEG with a tumor center below the EGJ should be categorized as a gastric cancer.<sup>[7]</sup> Thus, we used the IEBLD to assess the priority of LND for advanced type II and III AEG whose tumor epicenter is located below EGJ.

Most studies demonstrate that the incidence of LNM is highest in LN Nos. 1, 2, 3, and 7 and lowest in LN Nos. 5, 6, and 12a in type II/III AEG.<sup>[4,18,19,20]</sup> In this study, LN Nos. 1, 2, 3, and 7 had an higher metastatic rate, exceeding 20%, and LN Nos. 5, 6, and 12a had a very low metastatic rate in advanced AEG located below EGJ irrespective of the Siewert subgroups. The metastatic incidence at other stations differed between type II and III AEG. Goto et al.<sup>[19]</sup> determined that LN Nos. 9, 11p and 19 in type II/III AEG and LN No.4d in type III AEG exhibited a metastatic incidence of more than 10%. In the report by Hosokawa et al,<sup>[4]</sup> the incidence of Nos. 4, 8a, and 10 LNM was more frequent in type III tumors, and LNM in LN No. 9 was higher in type II tumors. However, Hasegawa et al.<sup>[18]</sup> reported that type III AEG yielded much higher metastatic rates in LN Nos. 4, 8a, 9, and 10 compared to type II tumors. These differences among different studies may be related to differences in the LND for each patient among the different studies. In the present study, neither the total number of dissected LNs nor the number of retrieved LNs at each station differed significantly between type II and III tumor groups. We found that the incidence of LNM for LN Nos. 9 and 11p was also higher than 10% in the 2 groups. The metastatic incidence at Nos. 4d, 8a, and 10 exceeded 10% only in type III AEG. Type III AEG seems to be more progressive than type II AEG, with larger tumor size, deeper invasion, less differentiation and more advanced stage. Therefore, more extensive LNM in type III AEG was observed, and patients with type III AEG had worse 5-year OS rates than those with type II AEG ( $P=.001$ ).

The beneficial effect of LND for Nos. 1, 2, 3, and 7 for type II/III AEG has been well documented and acknowledged.<sup>[21-23]</sup> Furthermore, the lack of therapeutic value in dissecting LN No. 5, 6, and 12a has also been confirmed by many studies.<sup>[4,19]</sup> However, for the remaining nodal stations, LND for stations with a higher incidence of LNM did not exhibit uniform beneficial effects. Hasegawa et al<sup>[18]</sup> reported that the IEBLDs of LN Nos. 8a and 9 were only 1.8 and 2.1, respectively. Hosokawa et al<sup>[4]</sup> also found that the IEBLD of No. 9 was only 1.5. Goto et al demonstrated that dissection of LN Nos. 9, 11p, and 19 would yield better therapeutic value (IEBLDs >3.0) for type II AEG,<sup>[22]</sup> whereas Yamashita et al<sup>[24]</sup> reported minimal LND effect with the exception of Nos. 1, 2, 3, and 7. A multicenter retrospective study from Japan reported that dissection of LN Nos. 4a and 11 could also obtain relatively higher survival benefits for advanced type II AEG.<sup>[25]</sup> For type III AEG, many studies have indicated that dissection of LN Nos. 9 and 11p would yield higher survival benefits, whereas LND for Nos. 4, 8a, and 10 seems to be more controversial.<sup>[4,18,19]</sup> The present study demonstrated that LND at Nos. 1, 2, 3, and 7 had greatest therapeutic benefit estimated by IEBLD for advanced type II/III AEG, consistent with previous reports. However, the IEBLDs of Nos. 4sa, 4sb, 5, 6, 11d, 12a, 19, and 20 were very low, suggesting that LND of these stations would not produce significant value for patients with AEG located below EGJ. Therefore, the IEBLD score for distal gastric LN (5, 6) supports the process of oesophagectomy in those patients not suitable for radical TG (RTG). Similarly the lack of benefit of dissection of stations 19/20 supports the RTG in siewert 2 and 3 without extending the dissection high into the chest which may increase its applicability in the higher BMI patients. We also observed that the IEBLDs of No.9 and 11p were

greater than 3.0 in both type II and III AEG, and the IEBLDs of No.4d and 8a were greater than 3.0 in type III tumors. Therefore, focusing on LND of paracardial LNs, lesser curvature LNs and LNs around the celiac axis (Nos. 7, 9, and 11p) is important for advanced type II/III AEGs located below the EGJ. Our results indicate that No. 10 lymphadenectomy for type III AEG may exhibit some therapeutic value (IEBLD=2.9). Given the complicated anatomy in the splenic hilar area and difficulty of performing No. 10 lymphadenectomy, whether No. 10 LND should be performed routinely for advanced type III AEG keeps controversial.<sup>[26,27]</sup> Yang et al<sup>[28]</sup> indicated that the difference in the 5-year survival rates of the patients who underwent No.10 lymphadenectomy vs those who did not undergo No.10 lymphadenectomy had no statistical significance ( $P=.342$ ). The new edition of the Japanese gastric cancer treatment guidelines<sup>[29]</sup> also did not recommend No.10 lymphadenectomy for AEG with a tumor diameter <4cm. In our study, the IEBLDs of No. 10 were greater than 4.0 in type III AEG patients with serosa-invasive tumors, undifferentiated tumors, macroscopic type 3-4 tumors and tumors  $\geq 50$  mm in size, suggesting relatively greater therapeutic benefit from No. 10 LND for these patients.

Our study has some limitations related to its single-center retrospective nature and small sample size. We evaluated the priority of LND by the IEBLD which could be influenced by the incidence of LNM. We did not perform LND to the same extent for each patient. For example, the number of dissected LNs were different among patients, while the metastatic rates could have been underestimated due to inappropriate LND. Besides, the analysis is not stratified conducted by different stages, which influences the LNM and lymphadenectomy. Moreover, there may have been a question in regard to the reliable incidence of No.10 LNM, because not all the patients received additional No. 10 lymphadenectomy. We only focus on eastern cohorts in this study. Western cohorts have a much higher BMI and particularly with Siewert 2, RTG may not be technically feasible so an Ivor Lewis Oesophagogastrctomy is performed. Hence, the applicability of the data or its reproducibility in western literature is uncertain. And Data to assess the effects of neoadjuvant therapy on lymph node yield and IELBD were not available in our centre, which is a another limitation of this study. Hence, the priority of LND for advanced AEG located below the EGJ must be confirmed in a further randomized prospective study.

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