

# Indication of Proximal Gastrectomy for Advanced Proximal Gastric Cancer Based on Lymph Node Metastasis at the Distal Part of the Stomach

Sejin Lee, MD,\*† Won Jeong Son, MS,‡ Yun Ho Roh, PhD,‡ Jeong Ho Song, MD,\*† Sung Hyun Park, MD,\*† Minah Cho, MD,\*† Yoo Min Kim, MD, PhD,\*† Woo Jin Hyung, MD, PhD,\*† and Hyoung-Il Kim, MD, PhD\*†

**Objective:** To suggest the possible indication of proximal gastrectomy for advanced gastric cancer located at the upper third of the stomach.

**Background:** Proximal gastrectomy has been an alternative surgical procedure for early proximal gastric cancer due to its benefits for quality of life while maintaining oncological outcomes. However, the oncological safety of proximal gastrectomy for advanced tumors remains unclear.

**Methods:** We retrospectively reviewed data from 878 patients who underwent radical total gastrectomy from 2003 to 2018 for pathologic T2–T4 gastric cancer in the upper third of the stomach. We identified risk factors for lymph node metastasis at the distal part of the stomach, which was not dissected in proximal gastrectomy. Subsequently, we evaluated the metastasis rate and therapeutic value index of lymph nodes at the distal part of the stomach in patients with none of these risk factors.

**Results:** Multivariable analysis revealed that esophagogastric junction (EGJ)-tumor epicenter distance >30 mm, tumor size >70 mm, macroscopic type IV tumor, and serosal invasion were risk factors for lymph node metastasis at the distal stomach. In patients without risk factors, the therapeutic value index for any lymph nodes at the distal stomach was 0.8, suggesting that lymph node dissection could be omitted in these patients.

**Conclusions:** EGJ-tumor epicenter distance ≤ 30 mm, tumor size ≤ 70 mm, not a macroscopic type IV tumor, and no serosal invasion could be an indication of proximal gastrectomy for advanced gastric cancer located at the upper third of the stomach.

## INTRODUCTION

Gastric cancer remains one of the most frequent cancers and the third leading cause of cancer-related mortality worldwide.<sup>1</sup> The frequency of proximal gastric cancer, including esophagogastric junction (EGJ) cancer, has been increasing in Western and Asian countries.<sup>2,3</sup> Operative options for treatment of proximal

gastric cancer are total gastrectomy and proximal gastrectomy. Total gastrectomy is widely accepted as a standard operation for proximal gastric cancer. However, almost all patients who undergo total gastrectomy experience weight reduction and all of them suffer from vitamin B12 deficiency.<sup>4,5</sup> Recent studies demonstrated that proximal gastrectomy provides patients with a better quality of life than total gastrectomy, in terms of weight loss and anemia.<sup>6,7</sup> Thus, considering the nutritional benefits of proximal gastrectomy, it would be preferable to recommend proximal gastrectomy for patients with gastric cancer located at the upper third of the stomach, if its oncological safety is ensured.

Korean and Japanese gastric cancer treatment guidelines suggest that proximal gastrectomy is an alternative procedure for early proximal gastric cancer due to its similar oncological outcomes compared with total gastrectomy.<sup>8,9</sup> However, the oncological safety of proximal gastrectomy for advanced proximal gastric cancer (APGC) remains unclear. The critical factor considered for the oncologic safety of proximal gastrectomy is the probability of lymph node (LN) metastasis at the distal part of the stomach (LN #4d, 5, and 6), which are not dissected during proximal gastrectomy. Although previous studies evaluated the metastasis rate and efficacy of dissection for LNs at the distal part of the stomach in APGC, few studies have identified risk factors for metastasis in these LNs.<sup>10–15</sup>

We hypothesize that proximal gastrectomy would be sufficient for radical LN dissection to ensure oncologic safety in patients with APGC who have a low risk of LN metastasis at the distal part of the stomach. In this study, we analyzed risk factors of LN metastasis at the distal part of the stomach in patients who underwent total gastrectomy for APGC. Based on the results of these analyses, we subsequently evaluated the therapeutic benefits of dissecting LNs at the distal stomach in patients with none of the risk factors.

From the \*Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea; †Gastric Cancer Center, Yonsei Cancer Center, Yonsei University Health System, Seoul, Republic of Korea; and ‡Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea.

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Reprint: Hyoung-Il Kim, MD, PhD, Department of Surgery, Yonsei University College of Medicine 50-1 Yonsei-ro Seodaemun-gu, Seoul, 03722, Republic of Korea. E-mail: [cairus@yuhs.ac](mailto:cairus@yuhs.ac)

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**METHODS**

**Patients**

We retrospectively reviewed a prospective database of 2313 patients who underwent total gastrectomy with LN dissection for gastric cancer in the upper third of the stomach. All procedures were performed from January 2003 to December 2018 at the Department of Surgery, Yonsei University College of Medicine. We included 1321 patients whose tumors were diagnosed pathologically as T2-T4. Individuals meeting any the following criteria were excluded from this study: distant metastases (n = 110), preoperative chemotherapy (n = 28), noncurative resection (n = 66), synchronous gastric cancer (n = 6), history of another cancer (n = 49), and incomplete pathologic data regarding the LN station (n = 184). A total of 878 patients were included in the final analysis (Fig. 1).

We collected preoperative patient information, including age, sex, body mass index (BMI), and American Society of Anesthesiologists classification, from our database. The Institutional Review Board of Severance Hospital, Yonsei University Health System approved the protocol (No. 4-2021-0336) and waived the requirement for informed consent for this retrospective study.

**Surgical Procedures**

Eight surgeons performed total gastrectomy via open, laparoscopic, or robotic approaches. According to the preoperative staging, the extent of LN dissection was D1+ for early gastric cancer and D2 for advanced gastric cancer.<sup>9</sup> D1+ dissection involved removal of the following LN bearing tissues: right pericardial LNs (LN #1); left pericardial LNs (LN #2); LNs along the lesser curvature (LN #3); left greater curvature LNs along the short gastric arteries (LN #4sa); left greater curvature LNs along the left gastroepiploic artery (LN #4sb); right greater curvature LNs along the right gastroepiploic artery (LN #4d); suprapyloric LNs (LN #5); infrapyloric LNs (LN #6); LNs along the left gastric artery (LN #7); LNs along the common hepatic artery (LN #8a); LNs around the celiac artery (LN #9); and LNs along the proximal splenic artery (LN #11p). D2 dissection involved removal of all LNs included in the D1+ dissection plus removal of LN-bearing tissues along the distal splenic artery (LN #11d), hepatic artery (LN #12a), and splenic hilum (LN #10). Based on the results of the JCOG0110 trial,<sup>16</sup> if the tumor invaded the greater curvature of the stomach or if LN metastasis was suspected around the splenic hilum, we performed splenic hilar LN dissection (LN #10) from 2017.

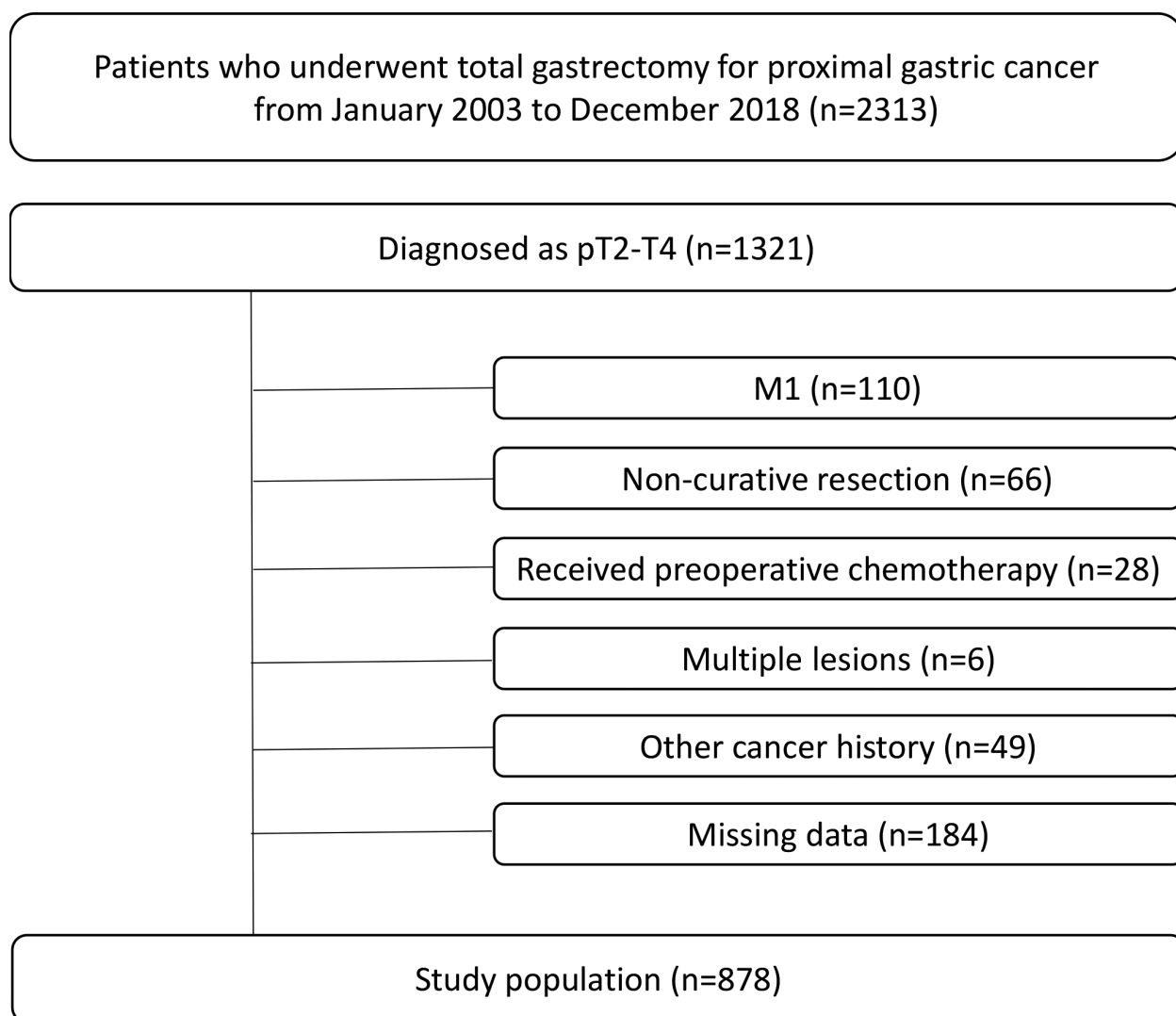


FIGURE 1. Flow diagram of the study.

### Pathologic Examination of Resected Stomach and LNs

After surgery, a surgeon separated the soft tissues containing LNs from the main specimen for each LN station. All nodal specimens and resected stomach were delivered to the pathology department after the operation. Pathologists obtained photographs of the resected stomach and recorded the tumor size and proximal and distal margins. Based on the pathologic and photographic findings, we measured the distance from the EGJ to the epicenter of the tumor. The tumor stage was defined according to the eighth edition of American Joint Committee on Cancer Staging System. Macroscopic type and histologic classification were also described, according to the Japanese Classification of Gastric Carcinoma (third English edition).<sup>17</sup>

### Therapeutic Value Index of Estimated Benefit From LN dissection

We used the therapeutic value index (TVI) as previously defined<sup>18</sup> to evaluate the benefit of dissecting LNs at the distal part of the stomach. The TVI was calculated by multiplying the incidence of LN metastasis at the station by the 5-year overall survival (OS) rate of patients with metastasis at that station. The incidence of LN metastasis and 5-year OS rate of patients with metastasis were calculated independently for each LN station.

### Statistical Analysis

Categorical variables were presented as frequency (percentage), and continuous variables were presented as mean (standard deviation [SD]). Univariable and multivariable logistic regression analyses were performed to identify risk factors for LN metastasis at the distal part of the stomach. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Optimal cutoff values were determined using Youden's index. The 5-year OS rate was calculated using the Kaplan–Meier method. All tests were two-sided, and  $P < 0.05$  was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software for Windows, version 25.0 (IBM Corp., Armonk, NY) and SAS for Windows, version 9.4 (SAS Inc., Cary, NC).

## RESULTS

### Clinicopathologic Characteristics

The mean patient age was 58.4 years (SD, 12.4), and the majority of patients were male (69.0%). The mean BMI was 23.3 kg/m<sup>2</sup> (SD, 3.0). The mean distance from EGJ to tumor epicenter was 35.4 mm (SD, 20.0), and the mean tumor size was 52.9 mm (SD, 33.0). A total of 114 patients (13.0%) had a macroscopic type IV tumor, and 626 patients (71.3%) had an undifferentiated tumor. The proportion of tumors invading the serosa was 44.5%, whereas 23.1% and 32.3% of tumors were pathologically T2 and T3, respectively. LN metastases were detected in 557 patients (63.4%), whereas 321 patients (36.6%) had no LN metastasis. A total of 101 patients (11.5%) had LN metastases at the distal part of the stomach, meaning any LN metastases at LN #4d, 5, and 6. The LN metastasis rates at LN #4d, 5, and 6 were 7.1, 3.8, and 4.4%, respectively (Table 1).

### Univariable Analysis to Identify Risk Factors for LN Metastasis at the Distal Part of the Stomach

In univariable analysis, LN metastasis at the distal part of the stomach was significantly associated with lower BMI ( $P = 0.004$ ), longer distance from EGJ to tumor epicenter ( $P < 0.001$ ), larger tumor size ( $P < 0.001$ ), macroscopic type

**TABLE 1.**

### Clinicopathologic Characteristics

Variables	Value (N = 878)
Age (y)	58.4 ± 12.4
Sex	
Male	606 (69.0)
Female	272 (31.0)
BMI (kg/m <sup>2</sup> )	23.3 ± 3.0
ASA classification	
1	356 (40.5)
2	413 (47.0)
3	100 (11.4)
4	9 (1.0)
Distance from EGJ to tumor epicenter (mm)	35.4 ± 20.0
Tumor size (mm)	52.9 ± 33.0
Tumor location, circular	
Lesser curvature	378 (43.1)
Greater curvature	93 (10.6)
Anterior wall	133 (15.1)
Posterior wall	245 (27.9)
Circular	29 (3.3)
Macroscopic type	
I	70 (8.0)
II	214 (24.4)
III	480 (54.7)
IV	114 (13.0)
Histologic type	
Differentiated	252 (28.7)
Undifferentiated	626 (71.3)
Pathologic T stage	
2	203 (23.1)
3	284 (32.3)
4	391 (44.5)
Pathologic N stage	
0	321 (36.6)
1	138 (15.7)
2	163 (18.6)
3a	167 (19.0)
3b	89 (10.1)
LN metastasis at the distal part of the stomach *	101 (11.5)
#4d	62 (7.1)
#5	33 (3.8)
#6	39 (4.4)

Data are presented as mean ± standard deviation or number (percentage).

\*Distal part of the stomach, which encompasses LN #4d, #5, and #6.

ASA indicates American Society of Anesthesiologists.

IV tumor ( $P < 0.001$ ), undifferentiated-type tumor ( $P = 0.001$ ), and serosal invasion ( $P < 0.001$ ) (Table 2).

### Cutoff Value Determination for Continuous Variables

We used Youden's index to determine optimal cutoff values for continuous variables associated with LN metastasis at the distal part of the stomach (BMI, tumor size, and EGJ–tumor epicenter distance). The optimal cutoff for BMI was 22 kg/m<sup>2</sup>, based on a maximum Youden's index of 21.89 kg/m<sup>2</sup>, and the optimal cutoff value for tumor size was 70 mm, based on a maximum Youden's index of 70.11 mm. The cutoff value for EGJ–tumor epicenter distance was 37.5 mm, based on a maximum Youden's index; however, this value was not practical for clinical applications. We therefore evaluated the LN metastasis rate and TVI according to EGJ–tumor epicenter distance (Table 3). The results showed that TVI at the distal part of the stomach was lowest (0.9) when the tumor epicenter was located within 30 mm from EGJ and highest ( $\geq 2.5$ ) when the epicenter was located within 40 mm or within 50 mm from EGJ. Based on these results, we set the cutoff value for EGJ–tumor epicenter distance as 30 mm.

**TABLE 2.**  
Univariable Analysis of Risk Factors for Lymph Node Metastasis at the Distal Part of the Stomach

Variables	OR	Univariable Analyses	
		95% CI	P
Age	0.984	0.968–1.000	0.052
Sex			
Male	Reference		
Female	1.400	0.910–2.154	0.126
BMI	0.899	0.836–0.966	0.004
ASA classification			
1	Reference		
2	1.010	0.649–1.574	0.964
3	0.950	0.469–1.923	0.886
4	0.960	0.117–7.875	0.970
Distance from EGJ to tumor epicenter	1.047	1.036–1.057	<0.001
Size	1.031	1.025–1.038	<0.001
Macroscopic type			
Not type IV	Reference		
Type IV	4.964	3.104–7.940	<0.001
Histologic type			
Differentiated	Reference		
Undifferentiated	2.744	1.529–4.924	0.001
Pathologic T stage			
2/3	Reference		
4	6.537	3.889–10.987	<0.001

ASA indicates American Society of Anesthesiologists.

**TABLE 3.**  
Comparison of Therapeutic Value Indices at the Distal Part of the Stomach According to Esophagogastric Junction–Tumor Epicenter Distance

EGJ–Tumor Epicenter Distance (mm)	Patients (n)	Metastatic rate at LN at Distal Stomach* (%)	5-year OS With LN Metastasis at Distal Stomach* (%)	Therapeutic Value Index
≤20	191	1.0	100	1.0
≤30	403	3.0	30.9	0.9
≤40	621	5.6	44.5	2.5
≤50	722	6.5	40.2	2.6

\*Distal part of the stomach, which encompasses LN stations #4d, #5, and #6.

**Multivariable Analysis to Identify Risk Factors for LN Metastasis at the Distal Part of the Stomach**

Using the cutoff values for BMI, tumor size, and distance from EGJ to tumor epicenter, we performed multivariable analysis to identify risk factors for LN metastasis at the distal part of the stomach. Multivariable analysis revealed that EGJ–tumor epicenter distance > 30 mm (*P* < 0.001), tumor size > 70 mm (*P* < 0.001), macroscopic type IV tumor (*P* = 0.022), and serosal invasion (*P* < 0.001) were independent risk factors for LN metastasis at the distal part of the stomach (Table 4).

**TVI With Regional LNs Among All Patients and Patients With None of Risk Factors**

A total of 247 patients (28.1%) had none of the 4 identified risk factors for LN metastasis at the distal part of the stomach. Specifically, they met these criteria: EGJ–tumor epicenter distance ≤ 30 mm; tumor size ≤ 70 mm; macroscopic type I, II, or III tumor (ie, not a type IV tumor); and no serosal invasion. In the patients with none of these risk factors, there was one patient with LN metastasis at LN #5 and one patient with LN metastasis at LN #6. None of the patients had LN metastasis at LN #4d. Calculated TVIs of LN #4d, #5, and #6 were 0, 0.4,

**TABLE 4.**  
Multivariable Analysis of Risk Factors for Lymph Node Metastasis at the Distal Part of the Stomach

Variables	OR	Multivariable Analyses	
		95% CI	P
BMI (kg/m <sup>2</sup> )			
≤22	Reference		
>22	0.715	0.447–1.144	0.162
Distance from EGJ to tumor epicenter (mm)			
≤30	Reference		
>30	3.456	1.772–6.742	<0.001
Size (mm)			
≤70	Reference		
>70	3.613	2.173–6.009	<0.001
Macroscopic type			
Not type IV	Reference		
Type IV	1.884	1.09–3.237	0.022
Histologic type			
Differentiated	Reference		
Undifferentiated	1.533	0.803–2.925	0.195
T stage			
2/3	Reference		
4	3.734	2.150–6.486	<0.001

and 0.4, respectively. TVI of being metastatic to any LN station among #4d, #5, and #6 was 0.8 (Table 5).

**DISCUSSION**

In this study, 4 risk factors, specifically longer distance from EGJ to tumor epicenter, larger tumor size, macroscopic type IV tumor, and serosal invasion, were risk factors for LN metastasis at the distal part of the stomach in patients with APGC. Approximately one-quarter of patients had no risk factors in the study population, and their TVIs at the distal part of the stomach were very low. Therefore, these results suggest that dissecting LNs at the distal part of the stomach is not essential for patients without risk factors. Hypothetically, the oncologic safety of proximal gastrectomy was not inferior to that of total gastrectomy for patients with APGC without risk factors.

The distance from EGJ to tumor epicenter had been the most relevant clinical parameter for surgical planning. For Siewert type II EGJ cancers, proximal gastrectomy is recommended as an acceptable procedure since the benefit of dissecting LNs at the distal part of the stomach is low for these tumors.<sup>13,15,19–22</sup> However, for advanced tumors located lower than Siewert type II, including Siewert type III EGJ cancers, the appropriate extent of gastric resection is controversial.<sup>15,19,21,22</sup> Our results demonstrate that proximal gastrectomy for advanced tumors would be an acceptable procedure for not only Siewert type II EGJ cancers but also for some patients with Siewert type III EGJ cancers, if the tumor epicenter is within 30 mm from EGJ.

The tumor size affects not only LN metastasis to the distal part of stomach but also the size of remnant stomach. Several studies have reported that the LN metastasis rate and TVI at the distal part of the stomach were low in advanced Siewert type II EGJ cancer, even though they included large tumors over 100 mm.<sup>13,15,19</sup> On the other hand, a prospective multicenter study in Japan reported that the LN metastasis rate at the distal part of the stomach was more than 10% in clinically advanced Siewert type II EGJ cancer, if the tumor size was more than 60 mm.<sup>23</sup> Based on the results of our study, we recommend total gastrectomy for large tumors due to the risk of LN metastasis at the distal stomach. Moreover, a larger tumor size results in a smaller remaining stomach volume after proximal gastrectomy, leading to poorer nutritional outcomes.<sup>24</sup> Insufficient remnant stomach volume reduces the nutritional advantages of proximal gastrectomy, even if oncologic safety is achieved.



**TABLE 5.**  
**Metastasis Rate, Survival of Patients With Nodal Metastasis, and Therapeutic Value Index of Lymph Node Stations for All and Patients With None of the Risk Factors**

Station No.	All Patients			Patients With None of the Risk Factors*		
	Metastasis Rate (%)	5-y OS of Patients With LN Metastasis (%)	Therapeutic Value Index	Metastasis Rate (%)	5-y OS of Patients With LN Metastasis (%)	Therapeutic Value Index
1	23.5	44.9	10.6	15.0	56.0	8.4
2	15	40.9	6.1	7.3	80.8	5.9
3	40.8	58.9	24.0	23.9	81.2	19.4
4sa	6	35.7	2.1	0	-	0
4sb	7.5	36.7	2.8	0.4	100	0.4
4d	7.1	34.5	2.4	0	-	0
5	3.8	29	1.1	0.4	100	0.4
6	4.4	32.7	1.4	0.4	100	0.4
7	15.4	51.1	7.9	6.1	73.3	4.5
8	8.2	37.3	3.1	2.8	100	2.8
9	133	48.1	6.4	7.7	57.4	4.4
10	29.1	28.8	8.4	20.8	100	20.8
11p	9.3	42.2	3.9	4.5	77.8	3.5
11d	4.2	59.3	2.5	2.8	100	2.8
12a	4.2	29.1	1.2	2.1	66.7	1.4

\*Patients with none of the risk factors: tumor size  $\leq$  70 mm, esophagogastric junction-tumor epicenter distance  $\leq$  30 mm, not a macroscopic type IV tumor, and no serosal invasion.

Serosal invasion, which is also a risk factor identified in this study, is corroborated by a previous study that reported LN metastasis at the distal part of the stomach in only T4 proximal gastric cancer.<sup>25</sup> Another study, which excluded T4 tumors and macroscopic type IV tumors, also demonstrated that LN metastasis rate at the distal part of the stomach was low and TVI was zero in APGC.<sup>10</sup> These 4 risk factors, EGJ-tumor epicenter distance, tumor size, macroscopic type, and serosal invasion can be assessed during preoperative investigations and intraoperative surgical findings.

Proximal gastrectomy is advantageous over total gastrectomy because of preservation of the distal portion of the stomach. The remaining distal stomach functions as a food reservoir to improve oral digestion and maintain weight after proximal gastrectomy.<sup>26</sup> Since the parietal cells essential for vitamin B12 absorption are located primarily in the body of the stomach, vitamin B12 supplements are required for life after total gastrectomy but are often not required after proximal gastrectomy.<sup>24</sup> Proximal gastrectomy also allows food passage through the duodenum, providing a route for iron absorption.<sup>27</sup> Given the advantages of function preservation and maintained oncologic safety, proximal gastrectomy would be preferable to total gastrectomy for patients with APGC and no risk factors.

No published prospective clinical trials have compared survival outcomes after proximal gastrectomy and total gastrectomy for APGC, although several retrospective reports have been published, as summarized in Supplement 1, <http://links.lww.com/AOSO/A86>.<sup>28–35</sup> Except for one report,<sup>30</sup> survival rates after proximal gastrectomy were comparable<sup>32–35</sup> or even better (although not significantly)<sup>28,29,31</sup> than those after total gastrectomy. However, it should be noted that esophageal reflux and anastomotic strictures were common after proximal gastrectomy.<sup>28,31</sup> Thus, a strategy to keep the motility of residual stomach, preserving more than half of the original stomach, is necessary.<sup>36</sup> Otherwise, protection of the esophageal mucosa using a flap formation<sup>37</sup> or double tract reconstruction should be considered.<sup>38</sup>

When applying our results as an indication for proximal gastrectomy, it will be necessary to evaluate metastasis at LN #3b (LNs along the right gastric artery located at the distal lesser curvature) because this station is not adequately dissected during proximal gastrectomy. The possibility of LN #3b metastasis was reported with APGC when tumor size was  $>40$  mm<sup>25</sup> or gastric invasion distance was  $>40$  mm.<sup>11</sup> In this study, we did not evaluate metastasis at LN #3b because the LN #3 is not

routinely separated into LN #3a and LN #3b in our practice. Thus, further investigations are necessary to evaluate metastasis at LN #3b when using our results as an indication for proximal gastrectomy.

Our study has the limitations of a retrospective study, including the potential for selection bias, which could limit the general applicability of our results. Randomized, prospective studies are required to assess the clinical applicability of these criteria. Moreover, we cannot evaluate survival outcomes of our indication for proximal gastrectomy, since all the patients underwent radical total gastrectomy. To identify long-term outcomes of our indication, future study is required comparing the patients who underwent total gastrectomy and proximal gastrectomy within the indication. Last, we analyzed risk factors for LN metastasis at the distal part of the stomach based on postoperative pathologic data, including EGJ-tumor epicenter distance, tumor size, macroscopic tumor type, and T stage. Although these risk factors can be assessed before or during surgery, accuracy of preoperative assessments was not considered in this study.

In conclusion, our results suggest that proximal gastrectomy may be indicated for APGC meeting all of these criteria: EGJ-tumor epicenter distance  $\leq 30$  mm, tumor size  $\leq 70$  mm, not a macroscopic type IV tumor (ie, types I, II, or III), and no serosal invasion. By performing proximal gastrectomy, it would be possible to provide a better quality of life while ensuring oncologic safety in patients meeting all four criteria.

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