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Original Article

Oncologic Feasibility of Proximal Gastrectomy in Upper Third Advanced Gastric and Esophagogastric Junctional Cancer

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ABSTRACT

Purpose: The aim of this study was to investigate the oncologic safety and identify potential candidates for proximal gastrectomy (PG) in upper third advanced gastric cancer (AGC) and esophagogastric junction (EGJ) cancers.
Materials and Methods: Among 5,665 patients who underwent gastrectomy for gastric adenocarcinoma between January 2011 and December 2017, 327 patients who underwent total gastrectomy with standard lymph node (LN) dissection for upper third AGC and Siewert type II EGJ cancers were enrolled. We analyzed the correlation between the metastatic rates of distal LNs (No. 4d, 5, 6, and 12a) around the lower part of the stomach and the clinicopathological characteristics. We identified subgroups with no metastasis to the distal LNs.
Results: The metastatic rate of distal LNs in proximal AGC and Siewert type II EGJ cancers was 7.0% (23 of 327 patients). On multivariate analysis, pathological T stage (P=0.001), tumor size (P=0.043), and middle third invasion (P=0.003) were significantly associated with distal LN metastases. Pathological 'T2 stage' (n=88), or 'T3 stage with ≤5 cm tumor size' (n=87) showed no metastasis in distal LNs, regardless of middle third invasion. Pathological T3 stage with tumor size > 5 cm (n=61) and T4 stage (n=91) had metastasis in the distal LNs.
Conclusions: In the upper third AGC and Siewert type II EGJ cancer, pathological T2 and small-sized T3 stage groups are possible candidates for PG in cases without distal LN metastasis. Further validation studies are required for clinical application.

Keywords: Gastrectomy; Gastric cancer; Esophagogastric junction; Lymph node

INTRODUCTION

Gastric cancer is a major global health problem and is the fifth most common cancer and the third most common cause of cancer-related mortality worldwide [1]. The incidence rate of gastric cancer is the highest in Asia, and Korea has the highest incidence rate in both sexes [2]. In western countries, proximal gastric cancers are common. However, in Korea, the most frequent site of gastric cancer is the lower third of the stomach. The incidence of proximal gastric cancer in Korea is approximately 7%–8%. However, antral cancer has decreased, but the incidence of cardia, fundus, and body cancer has increased because of westernization of

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Author Contributions

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Conflict of Interest

No potential conflicts of interest relevant to this article are reported.

the Korean diet, and people are gaining more weight, leading to an increase in the incidence of gastroesophageal reflux. In several studies, cardia cancer was positively associated with a westernized diet, obesity, and gastroesophageal reflux symptoms [3]. Therefore, we can predict that the incidence of upper third gastric cancer and esophagogastric junction (EGJ) cancer will increase in Korea.

According to the 2018 Japanese Gastric Cancer Treatment Guidelines (5th edition), total or distal gastrectomy is the standard surgical method for T2–T4 stage or lymph node (LN)-positive gastric cancers. Proximal gastrectomy (PG) can be applied exclusively to proximal cT1N0 gastric cancers or some early or advanced esophagogastric junctional cancers less than 4 cm in size, where more than half of the distal stomach can be preserved [4].

Previously, esophagogastrostomy was the mainstream reconstruction method after PG. Gastroesophageal reflux disease and reflux esophagitis were frequent complications because of the lack of a lower esophageal sphincter. These reflux symptoms could induce ulcers and stenosis in the esophagogastric anastomosis site, and total gastrectomy for remnant gastric cancer was performed because of these complications. A reconstruction method called jejunal interposition is available but it is too complicated to be performed laparoscopically, and may further lead to jejunal pouchitis. However, after the development of double tract reconstruction (DTR), food material can pass through 2 routes: the remnant stomach and the jejunum. Reflux esophagitis and gastroesophageal reflux disease after PG with DTR decreased to a level similar to that of total gastrectomy [5].

The advantages of preserving the distal stomach have been reported in many retrospective studies. Those who underwent PG had better body weight maintenance, prevention of postoperative anemia, and nutritional aspects, including vitamin B12, protein, albumin, and cholesterol levels, compared with those who underwent total gastrectomy [6-9].

Few studies have investigated the feasibility of PG in patients with proximal advanced gastric cancers. In PG, dissection of the distal LNs, such as No. 4d, 5, 6, and 12, around the lower part of the stomach is omitted. In terms of oncologic safety, patients without metastasis in LNs No. 4d, 5, 6, and 12 can be candidates for PG. In this single-center, large, retrospective study, we aimed to investigate the oncological safety of PG and identify potential candidates for PG in proximal advanced gastric cancer or Siewert type II EGJ cancer.

MATERIALS AND METHODS

Patients

Between January 2011 and December 2017, 5,665 patients with gastric cancer or EGJ cancer underwent gastrectomy with standard LN dissection at Seoul National University Hospital. Among the 5,665 patients, 651 underwent total gastrectomy for tumors located in the upper third of the stomach. We retrospectively reviewed the electronic medical records of 327 patients who had been diagnosed with pathological T2, T3, and T4 gastric cancer located in the upper third of the stomach or Siewert type II EGJ cancer and had undergone total gastrectomy with standard LN dissection. Patients who were diagnosed with pathologic T1 (n=267), received neoadjuvant chemotherapy (n=20), had multiple gastric cancers beyond the middle third area (n=19), had lower third invasion (n=11), neuroendocrine tumor (n=4), and restricted electronic medical records due to neuropsychiatric illness (n=3) were excluded (**Fig. 1**).

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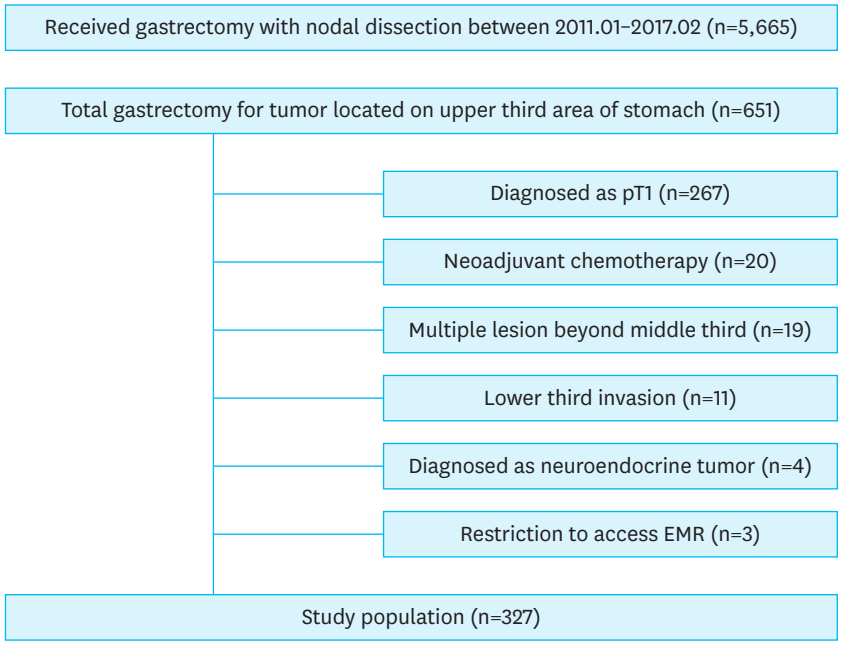

Fig. 1. Flow diagram of the study with 5,665 patients who had undergone gastrectomy with standard lymph node dissection for gastric cancer or Siewert type II esophagogastric junctional cancer between January 2011 and December 2017.
EMR = electronic medical record.

Human rights statement and informed consent

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later versions. As this study was retrospective, the need for informed consent was waived off, and the study was approved by the Institutional Review Board (IRB No. 2009-095-1157).

Clinical and pathological factors

We reviewed the following clinical and pathological factors: age, sex, pathological T stage, pathological N stage, tumor size (maximal tumor diameter), tumor location (tumor center located in the EGJ, or upper third of the stomach), histological type, presence or absence of vascular invasion, presence or absence of lymphatic invasion, and presence or absence of middle third invasion. The presence of middle third invasion was defined according to the pathology report, when the epicenter of a cancer located in the upper third area involved the middle third area. In previous studies, factors related to LN metastasis in early gastric cancer included tumor size, depth of invasion, histological type, presence or absence of vascular invasion, and lymphatic invasion [10-12]. Tumor location, depth, size, and histological type are also known to affect the incidence and distribution of LN metastasis in advanced gastric cancer [13,14]. Experienced pathologists determined the histopathological diagnoses. The cross-sectional, circumferential location of each tumor, degree of tumor progression, histological grade, and number of LN stations were defined according to the Japanese Gastric Cancer Association classification.

Description of the tumor location

After gastrectomy, we opened a fresh specimen and removed the LNs for pathological examination. The resected specimens were dissected, and tumor location and size were measured in all the specimens and recorded by the surgeon. The definition of true EGJ

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adenocarcinoma and its surgical treatment is controversial despite the revised tumor-node-metastasis classification [15,16]. Siewert classification is a well-known anatomical classification system for EGJ adenocarcinoma, and type II tumors have the epicenter 1 cm above and 2 cm below the EGJ [17]. In this study, the cancers with epicenter located more than 2 cm below the EGJ (including Siewert type III) were described as proximal gastric cancer.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software for Windows (version 25.0; IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using the χ^2 test and Fisher's exact test, and continuous variables were analyzed using the independent t-test. Logistic regression analysis was used for multivariate analysis to analyze the correlation between the metastatic rates of the distal LNs and several independent variables. Statistical significance was set at a P-value <0.05.

RESULTS

Clinicopathologic characteristics of patients

The number of patients who underwent radical gastrectomy with curative intent, between January 2011 and December 2017, was 5,665. A total of 327 patients who underwent total gastrectomy with standard LN dissection for proximal gastric cancer and Siewert type II EGJ cancer were included in this study. **Table 1** shows the background characteristics and histopathological findings of the patients.

The mean age was 61 years, and the male-to-female ratio was 2.4:1. Most patients had pathological stages T3 (45.3%) or N0 (35.5%). Stages II and III accounted for 82% of the cases.

Correlation between clinicopathologic factors and distal LN metastases

In univariate analysis, statistically significant factors related to distal LN metastases, such as tumor size, pathological T stage, histology, lymphatic invasion, vascular invasion, and middle third invasion were observed (**Table 2**). The differences between the 2 groups in terms of age, sex, and tumor location were not statistically significant. None of the patients with pT2 stage (n=88) had metastasis in the distal LNs. Distal LN metastasis occurred in 2.1% and 28.2% of patients with pT3 (n=148) and pT4 (n=91), respectively.

Pathological T stage, tumor size, and middle third invasion were statistically significant variables in the multivariate analysis (**Table 3**).

LN status according to tumor size and middle third invasion stratified with pT stage

Twelve subgroups were classified according to tumor size and middle third invasion, stratified by pathological T stage. The metastatic rates of each LN station were evaluated in the 12 groups. Patients were either classified as 'below' or 'above' based on tumor size of 5 cm, as the mean tumor size was 5.1 cm. In pathological T2 stage (n=88), there were no patients with metastasis in the distal LNs regardless of the tumor size and middle third invasion (**Table 4**). Pathological T3 patients with tumors ≤5 cm in size (n=87) had no distal LN metastasis. However, pathological T3 patients with tumors >5 cm in size (n=61) had distal LN metastasis (**Table 5**). All pathological T4 patients (n=91) had distal LN metastasis, regardless of the tumor size and presence or absence of middle third invasion (**Table 6**).

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Table 1. Patient demographics and tumor characteristics

Parameters	Values (n=327)
Age (yr)	
Median (range)	62 (21–83)
Mean±SD	60.9±11.4
Sex	
Male	231 (70.6)
Female	96 (29.4)
Pathological T stage	
T2	88 (26.9)
T3	148 (45.3)
T4	91 (27.8)
Pathological N stage	
N0	116 (35.5)
N1	60 (18.3)
N2	75 (22.9)
N3	76 (23.2)
Stage	
I	56 (17.1)
II	115 (35.2)
III	156 (46.8)
Tumor size (cm)	
Median (range): total	4.5 (0.8–16.0)
Mean±SD: total	5.1±2.5
Median (range): Proximal gastric cancer	4.5 (0.8–16.0)
Mean±SD: Proximal gastric cancer	5.1±2.6
Median (range): EGJ tumor	4.7 (2.5–13.5)
Mean±SD: EGJ tumor	5.3±2.3
Tumor location	
EGJ	55 (16.8)
High body (stomach)	272 (83.2)
Histology	
Differentiated	121 (37.0)
Undifferentiated	206 (63.0)
Vascular invasion	
No invasion	244 (74.6)
Invasion	83 (25.4)
Lymphatic invasion	
No invasion	134 (41.0)
Invasion	193 (59.0)
Middle third invasion	
No invasion	274 (83.8)
Invasion	53 (16.2)

Values are presented as number (%).
SD = standard deviation; EGJ = esophagogastric junction.

DISCUSSION

As LN metastasis is the most important prognostic indicator for gastric cancer, radical dissection of LNs is essential for gastric cancer treatment. In early gastric cancer located in the upper third area, PG is considered efficient because there is almost no metastasis to the distal LNs. However, total gastrectomy has been performed in more than 80% of proximal early gastric cancers because of severe reflux following direct esophagogastrostomy in PG. With the recent advent of DTR, reflux is no longer a problem, and PG is performed in an increasing number of cases of proximal early gastric cancer [18,19].

In contrast to early gastric cancer, total gastrectomy is the standard treatment for proximal advanced gastric cancer because metastasis can occur in the distal LNs. However, assuming

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Table 2. Clinicopathologic characteristics which were related to LN metastasis after total gastrectomy

Parameters	LN# 4d, 5, 6, 12 (–)	LN# 4d, 5, 6, 12 (+)	P-value
Age (yr)			0.299
Average	61.1	58.5	
Sex			0.554
Male	216	15	
Female	88	8	
Pathological T stage			<0.001
T2	88	0	
T3	145	3	
T4	71	20	
Tumor size (cm)			<0.001
Average	4.9	8.4	
Tumor location			0.392
EGJ	53	2	
HB	251	21	
Histology			0.001
Differentiated	120	1	
Undifferentiated	184	22	
Vascular invasion			<0.001
No invasion	235	9	
Invasion	69	14	
Lymphatic invasion			0.017
No invasion	130	4	
Invasion	174	19	
Middle third invasion			<0.001
No invasion	266	8	
Invasion	38	15	

LN = lymph node; EGJ = esophagogastric junction; HB = high body.

Table 3. Multivariate analysis of risk factors for lymph node metastasis after total gastrectomy

Parameters	Exp(B) 95% CI	P-value
Pathological T stage	10.075 (2.731–37.164)	0.001
Tumor size	3.958 (1.042–15.029)	0.043
Histology	3.879 (0.465–32.353)	0.210
Middle third invasion	4.610 (1.658–12.821)	0.003

CI = confidence interval.

that some advanced gastric cancers may not metastasize to distal LNs and PG could be performed in these selected patients, this study was performed to identify these candidates.

Pathological T stage, tumor size, tumor histology, presence of vascular or lymphatic invasion, or middle third invasion are known risk factors for LN metastasis in gastric cancer. Among these, T stage, tumor size, and middle third invasion were the most important independent risk factors for distal LN metastasis in this study. We performed logistic regression analysis on the metastasis rate to the distal LNs with 4 independent variables that were statistically significant in the univariate analysis. We excluded the presence or absence of vascular and lymphatic invasion in the logistic regression analysis. This study aimed to identify potential candidates for PG in patients with advanced proximal gastric and esophagogastric junctional cancer, but it is difficult to predict the presence or absence of vascular invasion and lymphatic invasion before performing surgery. Unlike these variables, pathological T stage, tumor size, histology, and presence or absence of middle third invasion can be predicted before surgery through esophagogastroduodenoscopy, endoscopic ultrasound, and computed tomography. Therefore, we analyzed the correlation between these factors and distal LN metastasis.

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Table 4. Lymph node status according to tumor size and middle third invasion stratified with pT2 stage

Station No.	Metastatic rate (%)				
	T2/B5/MTI (–)	T2/B5/MTI (+)	T2/A5/MTI (–)	T2/A5/MTI (+)	Total
1	11.3 (8/71)	0.0 (0/2)	8.3 (1/12)	0.0 (0/3)	10.2 (9/88)
2	4.2 (3/71)	0.0 (0/2)	8.3 (1/12)	0.0 (0/3)	4.5 (4/88)
3	16.9 (12/71)	50.0 (1/2)	41.7 (5/12)	33.3 (1/3)	21.6 (19/88)
4sa	1.4 (1/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	1.1 (1/88)
4sb	0.0 (0/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	0.0 (0/88)
4d	0.0 (0/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	0.0 (0/88)
5	0.0 (0/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	0.0 (0/88)
6	0.0 (0/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	0.0 (0/88)
7	4.2 (3/71)	50.0 (1/2)	25.0 (3/12)	0.0 (0/3)	8.0 (7/88)
8a	1.4 (1/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	1.1 (1/88)
9	5.6 (4/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	4.5 (4/88)
10	0.0 (0/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	0.0 (0/88)
11p	5.6 (4/71)	0.0 (0/2)	8.3 (1/12)	0.0 (0/3)	5.7 (5/88)
11d	1.4 (1/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	1.1 (1/88)
12a	0.0 (0/71)	0.0 (0/2)	0.0 (0/12)	0.0 (0/3)	0.0 (0/88)

B5 = below 5 cm; MTI = middle third invasion; A5 = above 5 cm.

Table 5. Lymph node status according to tumor size and middle third invasion stratified with pT3 stage

Station No.	Metastatic rate (%)				
	T3/B5/MTI (–)	T3/B5/MTI (+)	T3/A5/MTI (–)	T3/A5/MTI (+)	Total
1	19.8 (16/81)	16.7 (1/6)	34.6 (18/52)	44.4 (4/9)	26.4 (39/148)
2	13.6 (11/81)	0.0 (0/6)	28.8 (15/52)	0.0 (0/9)	17.6 (26/148)
3	39.5 (32/81)	0.0 (0/6)	42.3 (22/52)	55.6 (5/9)	39.9 (59/148)
4sa	1.2 (1/81)	0.0 (0/6)	5.8 (3/52)	0.0 (0/9)	2.8 (4/148)
4sb	2.5 (2/81)	0.0 (0/6)	1.9 (1/52)	0.0 (0/9)	2.7 (3/148)
4d	0.0 (0/81)	0.0 (0/6)	1.9 (1/52)	11.1 (1/9)	1.4 (2/148)
5	0.0 (0/81)	0.0 (0/6)	1.9 (1/52)	0.0 (0/9)	0.7 (1/148)
6	0.0 (0/81)	0.0 (0/6)	1.9 (1/52)	0.0 (0/9)	0.7 (1/148)
7	19.8 (16/81)	16.7 (1/6)	30.8 (16/52)	11.1 (1/9)	23.0 (34/148)
8a	3.7 (3/81)	0.0 (0/6)	5.8 (3/52)	0.0 (0/9)	4.1 (6/148)
9	8.6 (7/81)	0.0 (0/6)	9.6 (5/52)	0.0 (0/9)	8.1 (12/148)
10	2.5 (2/81)	0.0 (0/6)	7.7 (4/52)	0.0 (0/9)	4.1 (6/148)
11p	6.2 (5/81)	0.0 (0/6)	17.3 (9/52)	0.0 (0/9)	9.5 (14/148)
11d	0.0 (0/81)	16.7 (1/6)	9.6 (5/52)	0.0 (0/9)	4.1 (6/148)
12a	0.0 (0/81)	0.0 (0/6)	1.9 (1/52)	0.0 (0/9)	0.7 (1/148)

B5 = below 5 cm; MTI = middle third invasion; A5 = above 5 cm.

Table 6. Lymph node status according to tumor size and middle third invasion stratified with pT4 stage

Station No.	Metastatic rate (%)				
	T4/B5/MTI (–)	T4/B5/MTI (+)	T4/A5/MTI (–)	T4/A5/MTI (+)	Total
1	25.9 (7/27)	40.0 (2/5)	29.0 (9/31)	57.1 (16/28)	37.4 (34/91)
2	18.5 (5/27)	0.0 (0/5)	35.5 (11/31)	46.4 (13/28)	31.9 (29/91)
3	33.3 (9/27)	20.0 (1/5)	41.9 (13/31)	60.7 (17/28)	44.0 (40/91)
4sa	3.7 (1/27)	0.0 (0/5)	19.4 (6/31)	21.4 (6/28)	14.3 (13/91)
4sb	7.4 (2/27)	20.0 (1/5)	16.1 (5/31)	28.6 (8/28)	17.6 (16/91)
4d	3.7 (1/27)	20.0 (1/5)	12.9 (4/31)	46.4 (13/28)	20.9 (19/91)
5	0.0 (0/27)	0.0 (0/5)	6.5 (2/31)	10.7 (3/28)	5.5 (5/91)
6	0.0 (0/27)	20.0 (1/5)	0.0 (0/31)	10.7 (3/28)	4.4 (4/91)
7	14.8 (4/27)	60.0 (3/5)	45.2 (14/31)	35.7 (10/28)	34.1 (31/91)
8a	3.7 (1/27)	0.0 (0/5)	19.4 (6/31)	28.6 (8/28)	16.5 (15/91)
9	7.4 (2/27)	0.0 (0/5)	12.9 (4/31)	25.0 (7/28)	14.3 (13/91)
10	7.4 (2/27)	0.0 (0/5)	12.9 (4/31)	25.0 (7/28)	14.3 (13/91)
11p	11.1 (3/27)	20.0 (1/5)	16.1 (5/31)	25.0 (7/28)	17.6 (16/91)
11d	3.7 (1/27)	0.0 (0/5)	12.9 (4/31)	14.3 (4/28)	9.9 (9/91)
12a	3.7 (1/27)	0.0 (0/5)	0.0 (0/31)	7.1 (2/28)	3.3 (3/91)

B5 = below 5 cm; MTI = middle third invasion; A5 = above 5 cm.

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There have been few studies on PG in advanced gastric cancer. Rosa et al. [20] reported that there were no differences in the 5-year survival rates and major postoperative complications between the PG and total gastrectomy groups in upper third gastric cancer, regardless of the T stage. Sugoor et al. [21] reported that the estimated 2-year overall survival rates were 73.8% and 49.9% in the PG group and the total gastrectomy group. Yura et al. [22] reported that the metastatic rates of distal LNs in proximal T2/T3 gastric cancer were very low, and the therapeutic indices were zero. Therefore, they concluded that PG could be oncologically safe for patients with pT2/T3 proximal gastric cancer. Previous studies have been related to pathological T stage, TNM stage, or overall survival rate. However, this study differs from earlier studies because various variables and specific potential candidates for PG were analyzed. In addition, a previous study showed that the remnant stomach size and quality of life after gastrectomy were related [23]. Therefore, it may be meaningful to consider tumor size and middle third invasion of the stomach before PG.

Regarding EGJ type II cancer, the epicenter of which is located within 2 cm of the EGJ, there is no consensus on the type of resection and extent of lymphadenectomy. PG with or without lower esophageal resection, total gastrectomy with or without lower esophageal resection, esophageal resection, and upper gastric resection can be selected for esophagogastric junctional cancer according to the clinical situations. This study is important as it further clarifies the "clinical situation." In addition, according to the newly released Japanese Gastric Cancer Association Guideline, PG can be applied in advanced Siewert type II EGJ cancer if the tumor size is less than 4 cm [24], which is consistent with our findings as there was no metastasis to distal LNs in some advanced EGJ cancers.

The present study had some limitations. First, this study was retrospective and was performed using single-center database. Second, it is not possible to know the exact pathological stage of cancer before gastrectomy. Only the clinical stage can be predicted through several radiologic examinations before surgery. There are many differences in the clinical staging methods of gastric cancer among medical centers worldwide, and the accuracy of clinical T staging varies greatly with the methods. In previous studies, the accuracy of EUS-guided T-staging ranged from 60% to 90% [25]. The accuracy of pathological stages T1 and T2 for gastric cancer by spiral CT was approximately 42.86%. Spiral CT imaging has a greater advantage in the evaluation of the T stage of gastric cancer in the pathological T3 and T4 stages, with an accuracy of approximately 89% to 98% [26]. Therefore, an accurate and internationally uniform clinical staging method should be developed to evaluate the correlation between the clinical T stage and metastatic rate of distal LN metastasis. However, in some cases, PG was performed in patients diagnosed with early gastric cancer in the preoperative phase, but in the final pathology report, it may appear as T2 or T3. In these cases, there is a dilemma regarding the need for the removal of distal LNs with additional surgery. However, our results can help determine the need for additional surgery. If we can create a nomogram with independent risk factors to identify the group without distal LN metastasis and select the candidates for PG, it will be more clinically useful. Validation studies should be conducted in other medical institutes to generalize the clinical application of this result. Third, the data for LN No. 3 could not be analyzed separately for No. 3a and 3b. PG would be oncologically appropriate for cases that do not require LN No. 3b dissection because dissection of LN No. 3 is incomplete at the distal extent of PG [27]. Analyzing LN No. 3a and 3b in separate studies may be helpful in confirming the oncological safety of PG.

In conclusion, patients with pathological T2 stage or pathological T3 stage with small tumor size can be candidates for PG with standard LN dissection in terms of oncological safety.

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