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Long-Term Outcomes and Risk Factors for Lymph Node Metastasis in Siewert Type II/III Early Gastric Cancer

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Objectives: The incidence of adenocarcinomas of the esophagogastric junction (EGJ) and cardia has been gradually increasing in the East. Cancers of the EGJ and gastric cardia have poor prognoses. This study aimed to investigate lymph node metastasis (LNM) rates, their predictive factors, and determine the long-term outcomes of patients with Siewert type II/III early gastric cancer (EGC). **Methods:** Between January 2014 and June 2022, a total of 573 patients with gastric cancer, including 130 with Siewert type II/III EGC, underwent total gastrectomies at the Kosin University Gospel Hospital. Factors associated with LNM were analyzed using a logistic regression model. **Results:** Of the 130 patients with Siewert type II/III EGC, 10 (7.7%) demonstrated LNM (LNM-positive group). Macroscopically elevated lesions (I+IIa) (60.0% vs. 16.7%; p=0.009) and lymphovascular invasion (70.0% vs. 5.8%; p<0.001) were more common and the depth of invasion was deeper (p=0.003) in the LNM-positive patients than in the LNM-negative group. Multivariate analysis showed that macroscopically elevated lesions (odds ratio [OR], 19.48; 95% confidence interval [CI], 1.93–197.11; p=0.012) and lymphovascular invasion (OR, 52.63; 95% CI, 5.26–526.51; p=0.001) were associated with LNM. Kaplan–Meier analysis revealed that the 5-year overall and disease-specific survival rates of patients with Siewert type II/III EGC were 90.0% and 98.9%, respectively. During a median follow-up period of 49 months (range, 12–122 months), one patient (0.8%) died owing to gastric cancer recurrence. **Conclusions:** Patients with Siewert type II/III EGC showed favorable long-term outcomes. Macroscopically elevated lesions and lymphovascular invasion are associated with LNM.

Keywords Stomach neoplasms; Esophagogastric junction; Lymphatic metastasis; Treatment outcome.

INTRODUCTION

In recent years, the incidence of adenocarcinomas of the esophagogastric junction (EGJ) and cardia has dramatically increased worldwide.[1-3] These adenocarcinomas present significant challenges for physicians because of their unique characteristics. For endoscopists, these adenocarcinomas are difficult to detect early and are technically difficult to access and evaluate. Endoscopic procedures, such as endoscopic submucosal dissection (ESD), can be performed to treat early adenocarcinomas of the EGJ and cardia. However, more advanced cases require invasive surgery, such as total gastrectomy, which can be burdensome for both patients and surgeons. In addition, the area near the EGJ contains the main lymphatic drainage from the mediastinal and abdominal fields, increasing the risk of lymph node (LN) metastasis (LNM).[4] As a result, pa-

tients with adenocarcinomas of the EGJ and cardia have worse prognoses than those with adenocarcinomas arising from the gastric body or antrum.[5] Because of these characteristics of EGJ adenocarcinomas, Siewert and Stein[6] suggested the classification of EGJ adenocarcinoma into types I, II, and III. In April 1997, the second International Gastric Cancer Congress approved the Siewert classification for EGJ adenocarcinoma.[7] Today, the Siewert classification is widely accepted in clinical practice.

Although Siewert type I EGJ cancer is more prevalent in Western countries than in Eastern countries, Siewert type II/III EGJ cancer is more prevalent in Eastern countries.[8] Siewert type I cancers are generally categorized as esophageal cancers whereas Siewert type II/III cancers are classified as gastric cancers.[8,9] As mentioned earlier, endoscopic procedures, such as ESD, are used to treat early gastric cancer (EGC). However, a subset of EGCs exhibit LNM, which is directly associated with patient prognosis. Although the indications for ESD in EGCs have expanded, the decision to perform ESD is often challenging because of its specificity, especially for cancers of the EGJ and cardia. Therefore, this study aimed to determine the rate of LNM in Siewert type II/III EGC, the factors affecting LNM, and the long-term survival of patients diagnosed with Siewert II/III EGC.

METHODS

Study population and data collection

The medical records of patients with Siewert type II/III adenocarcinomas who underwent total gastrectomies between January 2014 and June 2022 at Kosin University Gospel Hospital were retrospectively reviewed. The exclusion criteria included advanced gastric adenocarcinoma, history of previous gastric cancer, history of previous gastric surgery, and diagnosis of other gastric malignancies (including gastric neuroendocrine and gastrointestinal stromal tumors). Within the target study period, 573 patients underwent total gastrectomy for gastric cancer at our hospital. Among them, 130 had Siewert type II/III EGC.

Baseline demographic data, such as alcohol consumption, smoking habits, family history of gastric cancer, hypertension, and diabetes mellitus were recorded. Pathological data included tumor size, differentiation, depth of invasion, presence of lymphovascular invasion, number of dissected LNs, and presence of LNM. Survival was monitored until April 2024. For patients who died at the Kosin University Gospel Hospital, we determined the time and cause of death. For patients lost to follow-up, we verified their National Health Insurance status. If their National Health Insurance was terminated, they were considered deceased. In these cases, the next of kin were contacted by telephone to verify the causes of death of the deceased patients. The study protocol was approved by the Institutional Review Board of Kosin University Gospel Hospital (approval number: 2024-07-019); the requirement for written informed consent was waived owing to the retrospective nature of the study. The study was performed in accordance with the guidelines of the Declaration of Helsinki.

Endoscopic examination and surgical procedure

All participants underwent esophagogastroduodenoscopy, and all were asked to refrain from food and water intake for at least 8 h prior to the procedure. Endoscopic findings were categorized as elevated (I+IIa), flat (IIb), or depressed (IIc+III), based on the Japanese Gastric Cancer Guidelines.[10]

Based on the endoscopic findings and the pathologic location of the resected specimen, EGJ adenocarcinomas were classified according to the Siewert classification: 1) Siewert type I: the epicenter of the tumors was located 1–5 cm above the EGJ, regardless of EGJ involvement; 2) Siewert type II: the epicenter of the tumors was located between 1 cm above and 2 cm below the EGJ, with EGJ involvement; and 3) Siewert type III: the epicenter of the tumors was located 2–5 cm below the EGJ, with EGJ involvement.[6]

During the study period, all patients with gastric adenocarcinoma of the upper body, cardia, or EGJ underwent total gastrectomies. None of the patients underwent other operations, such as proximal gastrectomy. The extent of LN dissection (D1, D1+, D2, and D2+) was based on the Japanese Gastric Cancer Treatment Guidelines.[11] D2 or D2+ LN dissection was performed if nodal involvement was suspected. Roux-en-Y reconstruction was performed after the total gastrectomy.

Pathologic evaluation

Gastric adenocarcinomas were categorized as differentiated (including well-differentiated, moderately differentiated, or papillary adenocarcinoma) or undifferentiated (including poorly cohesive adenocarcinoma or signet ring cell carcinoma).[12] Gastric adenocarcinomas with both differentiated and undifferentiated components were categorized depending on the quantitatively predominant pathologic type.[13] Tumor size was based on the maximum diameter of the tumors. Submucosal invasion was categorized as "upper third" (submucosa [SM] 1, submucosal invasion <500 μm from the muscularis mucosae), "middle third" (SM 2, 500–999 μm from the muscularis mucosae), and "lower third" (SM 3, ≥1000 μm from the muscularis mucosae). The resected EGC specimens were serially sectioned at 3-mm intervals, and complete histopathological examinations were conducted by expert pathologists. For tu-

mor/node/metastasis (TNM) staging, the 8th edition of the American Joint Committee on Cancer TNM Staging Manual for esophageal and gastric cancers was adopted.[14]

Statistical analysis

Categorical data are presented as numbers (%). The chi-squared (χ^2) or Fisher exact test was used to compare proportions of categorical parameters. Continuous data are shown as means (±standard deviation) and analyzed using the Student t-test or Mann–Whitney U test. Multivariate logistic regression analysis was used to evaluate the relationship between LNM and other clinicopathological factors, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Survival analyses were performed using the Kaplan–Meier method. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software, Version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

The baseline patient characteristics are presented in Table 1. The mean patient age was 63.3 years (range, 37–83 years), and 84 patients (64.6%) were males. Siewert type II EGC was diagnosed in 52 (40.0%) patients; 78 (60.0%) had Siewert type III EGC. The proportions of gastric cancer invasion depths were 17.7%, 17.7%, 13.8%, 21.5%, and 29.2% for lamina propria, muscularis mucosa, SM 1, SM 2, and SM 3, respectively. The percentage of patients with lymphovascular invasion was 10.8%.

Of the 130 patients included in the study, 10 (7.7%) were positive for LNM. Endoscopic findings, the depth of cancer invasion, and lymphovascular invasion were associated with LNM. However, there were no significant differences in LNM based on the Siewert type, tumor size, or histology (Table 1).

Risk factors for LNM in Siewert type II/III EGC

The factors related to LNM in patients with Siewert type II/III EGC are presented in Table 2. Univariate logistic regression analysis showed that the endoscopically elevated type (I+IIa) (p=0.004), SM 2+3 cancer invasion (p=0.032), and lymphovascular invasion (p<0.001) were associated with positive LNM. Multivariate logistic regression analysis revealed that an endoscopically determined elevated type lesion (I+IIa) (OR, 19.48; 95% CI, 1.93–197.11) and lymphovascular invasion (OR, 52.63; 95% CI, 5.26–526.51) were associated with LNM.

LNM rate according to tumor size and depth of submucosal invasion in T1b Siewert II/III cancer

Generally, differentiated-type SM 1 gastric cancer <30 mm is considered an expanded indication for ESD. Therefore, we evaluated the LNM rate in accordance with tumor size and depth of submucosal invasion (Table 3). The LNM rates were 5.6% (1/18), 7.1% (2/28), and 18.4% (7/38) for SM 1, SM 2, and SM 3, respectively. The highest rate of LNM was identified in the group with SM 3 invasion measuring 31–40 mm (75.0%, 3/4) and the lowest rate of LNM was identified in the group with SM 1 invasion measuring 11–20 mm (20.0%, 1/5).

Long-term survival of patients with Siewert types II and III EGC

Among the 10 patients with LNM, 4 (40.0%) underwent adjuvant chemotherapy. The 5-year overall, disease-specific, and recurrence-free survival rates of patients with Siewert type II/III EGC were 90.0%, 98.9%, and 99.2%, respectively (Fig. 1A). In terms of LNM, there was no significant difference in the 5-year survival rates between the LNM-negative (90.2%) and LNM-positive (87.5%) groups (p=0.865) (Fig. 1B). The survival rates of patients with Siewert type II/III EGC and LNM are shown in Table 4.

Of the 130 patients, 12 (9.2%) died during a median follow-up period of 49 months (range, 12–122 months). Among them, only one (0.8%) had gastric cancer recurrence (peritoneal cancer) after the total gastrectomy (32 months later); the patient died from the gastric cancer. The patient had an adenocarcinoma lesion about 3.0×1.5 cm in size that was moderately differentiated, without LNM but with cancer involvement at the specimen margin at the time of surgery. The depth of invasion was SM 3, and the proximal safety margin was 0.5 cm, close to the carcinoma.

DISCUSSION

The global incidence of gastric adenocarcinoma has rapidly declined over the last few decades.[15] However, the incidence of adenocarcinomas of the gastric cardia and EGJ is increasing in both Western and Eastern countries.[1,2] The results of this study revealed that macroscopically elevated lesions and pathologic lymphovascular invasion could be risk factors for LNM in patients with Siewert type II/III EGC. Additionally, these patients presented with favorable long-term survival, regardless of LNM.

LNM is strongly associated with gastric cancer prognoses. This study demonstrates that lymphovascular invasion and macroscopically elevated lesions are associated with LNM in Siewert type II/III EGC. Lymphovascular invasion is a well-

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Table 1. Baseline characteristics of patients with Siewert type II/III early gastric cancer

Characteristics	Patients (n=130)	LNM (-) (n=120)	LNM (+) (n=10)	*p*-value
Age (yr)	63.3±9.1	63.2±9.2	63.9±9.3	0.821
Sex				0.742
Male	84 (64.6)	78 (65.0)	6 (60.0)	
Female	46 (35.4)	42 (35.0)	4 (40.0)	
Cigarette smoking	49 (37.7)	46 (38.3)	3 (30.0)	0.318
Alcohol intake	49 (37.7)	47 (39.2)	2 (20.0)	>0.999
Gastric cancer family history	18 (13.8)	18 (15.0)	0 (0.0)	0.356
Hypertension	55 (42.3)	50 (41.7)	5 (50.0)	0.742
Diabetes mellitus	36 (27.7)	32 (26.7)	4 (40.0)	0.462
Siewert type				0.197
II	52 (40.0)	46 (38.3)	6 (60.0)	
III	78 (60.0)	74 (61.7)	4 (40.0)	
Endoscopic finding				0.009*
Elevated (I+IIa)	26 (20.0)	20 (16.7)	6 (60.0)	
Flat (IIb)	21 (16.2)	21 (17.5)	0 (0.0)	
Depressed (IIc+III)	83 (63.8)	79 (65.8)	40 (40.0)	
Ulcer	27 (20.8)	26 (21.7)	1 (10.0)	0.687
Extent of nodal dissection				0.691
D1	4 (3.1)	4 (3.3)	0 (0.0)	
D1+	54 (41.5)	50 (41.7)	4 (40.0)	
D2	71 (54.6)	65 (54.2)	6 (60.0)	
D2+	1 (0.8)	1 (0.8)	0 (0.0)	
Dissected lymph nodes (n)	34.8±12.7	35.1±12.9	31.7±10.9	0.427
Tumor size (mm)	26.7±16.4	26.1±16.5	33.2±14.7	0.191
Histology				0.511
Differentiated	58 (44.6)	55 (45.8)	3 (30.0)	
Undifferentiated	72 (55.4)	65 (54.2)	7 (70.0)	
Depth on invasion				0.003*
LP	23 (17.7)	23 (19.2)	0 (0.0)	
MM	23 (17.7)	23 (19.2)	0 (0.0)	
SM 1	18 (13.8)	17 (14.2)	1 (10.0)	
SM 2	28 (21.5)	26 (21.7)	2 (20.0)	
SM 3	38 (29.2)	31 (25.8)	7 (70.0)	
Lymphovascular invasion	14 (10.8)	7 (5.8)	7 (70.0)	<0.001†

Data are presented as mean±standard deviation or n (%).
*p<0.05, linear-by-linear association test; †p<0.05, Fisher exact test.
SM 1, submucosal invasion <500 μm from the muscularis mucosae; SM 2, submucosal invasion 500–999 μm from the muscularis mucosae; SM 3, submucosal invasion ≥1000 μm from the muscularis mucosae; LNM: lymph node metastasis; LP, lamina propria; MM, muscularis mucosa; SM, submucosa.

known risk factor for LNM in most cancer types. However, the reported macroscopic features associated with LNM vary across studies. Macroscopically elevated lesions have been found to be preoperative predictors of ESD or lymphovascular invasion for EGC,[16] consistent with the results of the current study. In contrast, Chu et al.[17] reported that macroscopically elevated lesions were significantly associated with LNM in 1262 patients with EGC.

The decision to perform ESD on lesions presumed to be EGC and located in the EGJ or gastric cardia is difficult for both physicians and patients. According to the recent Japanese Gastric Cancer Treatment Guidelines, endoscopic curability "B" for pT1b cancer, an expanded indication for ESD, is assigned when all the following conditions are fulfilled: en bloc resection, histologically differentiated type-dominant, SM 1 (<500 μm from the muscularis mucosae), negative horizontal and vertical margins, no lymphovascular invasion, and tumor size ≤3 cm.[18] Relative to the histology and size of the cancer lesion, none of

Table 2. Factors predicting lymph node metastasis in patients with Siewert type II/III early gastric cancer

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value*
Age	1.01	0.94–1.08	0.820	0.98	0.90–1.07	0.626
Sex			0.751			0.566
Male	1			1		
Female	1.24	0.33–4.63		1.81	0.24–13.70	
Siewert type			0.190			
II	1					
III	0.41	0.11–1.55				
Endoscopic finding			0.004†			0.012†
Flat/depressed (IIb+IIc+III)	1			1		
Elevated (I+IIa)	7.50†	1.94–29.02†		19.48†	1.93–197.11†	
Tumor size	1.02	0.99–1.05	0.170			
Histology			0.341			
Differentiated	1					
Undifferentiated	1.97	0.49–8.00				
Depth on invasion			0.032†			0.229
SM 1	1			1		
SM 2+3	9.95†	1.22–80.97†		4.30	0.40–46.36	
Lymphovascular invasion	37.67†	7.97–178.01†	<0.001†	52.63†	5.26–526.51†	0.001†

*p<0.05, multivariate logistic regression test, with logistic model including age, sex, endoscopic findings, depth of invasion, and lymphovascular invasion; †Statistical significance.
SM 1, submucosal invasion <500 μm; SM 2+3, submucosal invasion ≥500 μm; OR, odds ratio; CI, confidence interval; SM, submucosa.

Table 3. Lymph node metastasis rates according to tumor size and depth of submucosal invasion in pT1b Siewert type II/III cancer

	SM 1	SM 2	SM 3
Tumor size			
≤10 mm	0/4 (0)	0/2 (0)	0/0 (0)
11–20 mm	1/5 (20.0)	0/11 (0)	0/12 (0)
21–30 mm	0/4 (0)	1/8 (12.5)*	3/11 (27.3)*
31–40 mm	0/2 (0)	0/3 (0)	3/4 (75.0)
≥41 mm	0/3 (0)	1/4 (25.0)*	1/11 (9.1)
Cumulative total	1/18 (5.6)	2/28 (7.1)	7/38 (18.4)

Data are presented as n (%).
*Patients with differentiated adenocarcinoma are included.
SM 1, submucosal invasion <500 μm; SM 2, submucosal invasion 500–999 μm; SM 3, submucosal invasion ≥1000 μm; SM, submucosa.

the patients with Siewert type II/III EGC, in this study, included in either the absolute or expanded indications for ESD developed LNM. One patient with LNM and SM 1 invasion also exhibited lymphovascular invasion. These results align with previous studies evaluating the indications for ESD based on the risk of LNM in patients with Siewert type II/III EGC.[19,20] One meta-analysis of studies involving ESD for early stage EGJ cancer reported the absence of local recurrence or distant metastasis for the 269 lesions treated with curative resection.[20] Thus, Siewert type II/III EGC, which is considered under the gastric scheme, may follow the ESD indications appropriate for other gastric cancer types.

Cancers of the EGJ and gastric cardia have different biological characteristics (e.g., ethnicity, geography, and socioeconomic status) compared with non-cardia gastric cancers.[21] In addition to the aforementioned major LN drainage pathways, cardia cancer is more frequently a gastric carcinoma involving lymphoid stroma than are non-cardia cancer types; thus, they have a higher propensity for submucosal invasion.[22] The prognoses of patients with cancers of the EGJ and gastric cardia are known to be worse than for those with non-cardia cancers. Although well-designed clinical trials comparing the survival of patients with EGJ and gastric cancers are limited, Petrelli et al.[5] published a meta-analysis on this issue. They analyzed 50 studies, comprising 128268 patients, involving cancers located in proximal stomach and reported that these were associated with a significantly increased risk of all-cause mortality (hazard ratio, 1.31; 95% CI, 1.17–1.46; p<0.001; I^2=91%). Additionally, some studies have reported a 5-year overall survival rate of approximately 50% for patients with locally advanced EGJ cancer.[23] However, the prognosis of patients with EGJ and gastric cardia cancers showed a significant difference depending on whether the cancer was detected early or at an advanced stage. In their study, the 5-year overall and disease-specific survival rates for patients with Siewert type II/III EGC

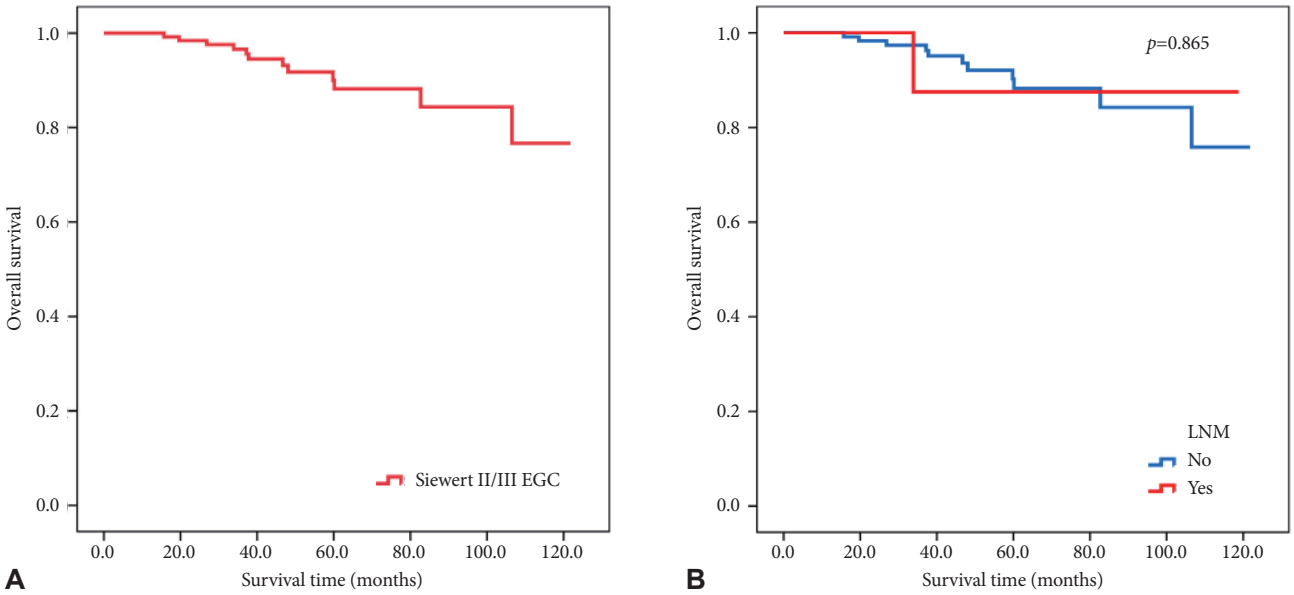

Fig. 1. Kaplan–Meier estimate of overall survival for patients with Siewert type II/III EGC (A) and overall survival for those with LNM (B). EGC, early gastric cancer; LNM, lymph node metastasis.

Table 4. Summary of patients with lymph node-positive Siewert type II/III early gastric cancer

Case	Age (yr)	Sex	Siewert type	Endoscopic findings	Ulcer	Tumor size (mm)	Histology	ESD criteria	Depth of invasion	Lymphovascular invasion	Adjuvant chemotherapy	Follow-up period (months)	Survival
1	72	M	III	IIa	-	38	PD	Beyond	SM 3	-	+	119	Yes
2	74	M	II	IIa	+	40	Cohesive	Beyond	SM 3	+	+	34	No (due to HCC)
3	70	F	III	IIc	-	25	SRC	Beyond	SM 3	-	+	71	Yes
4	54	M	II	IIa	-	25	PD	Beyond	SM 3	-	-	57	Yes
5	56	F	II	IIa	-	65	MD	Beyond	SM 2	+	-	74	Yes
6	68	F	III	I	-	23	MD	Beyond	SM 2	+	-	43	Yes
7	69	M	II	IIc	-	31	PD	Beyond	SM 3	+	-	12	Yes
8	60	M	II	III	-	12	PD	Beyond	SM 1	+	-	53	Yes
9	46	F	III	IIc	-	45	Cohesive	Beyond	SM 3	+	+	47	Yes
10	70	M	II	IIa	-	28	MD	Beyond	SM 3	+	-	19	Yes

SM 1, submucosal invasion <500 μm; SM 2, submucosal invasion 500–999 μm; SM 3, submucosal invasion ≥1000 μm; ESD, endoscopic submucosal dissection; PD, poorly differentiated; SRC, signet ring cell; MD, moderately differentiated; SM, submucosa; HCC, hepatocellular carcinoma.

were 90.0% and 98.9%, respectively. In this study, only one patient (0.8%) died owing to the recurrence of gastric cancer. Pyo et al.[19] reported that the 5-year overall, disease-specific, and recurrence-free survival rates in patients with Siewert type II/III EGC are 96.3%, 98.6%, and 99.0%, respectively. A retrospective multicenter cohort study from Japan also reported that the 5-year EGJ cancer-specific survival rate is 95.1% for stage I EGJ adenocarcinoma.[24] Therefore, patients identified as having EGC can be surveyed similarly to those with non-cardia EGC, even if the cancer originates in the EGJ and cardia.

The present study had several limitations. First, this was a retrospective single-center study that included only a small number of patients with LNM. Second, lymphadenectomy was performed according to the clinical condition and each patient's cancer stage. However, owing to the retrospective design of this study, the extent of lymphadenectomy was inconsistent. Third, although the long-term survival of patients with Siewert type II/III EGC was investigated, no comparison was made between Siewert type II/III EGC and non-cardia EGC. Nevertheless, the clinicopathological factors of patients with Siewert type II/III EGC included in this study were comprehensively investigated, and various methods, such as National

Health Insurance and telephone research, were used to determine patient survival. Therefore, our results provide detailed information regarding the prognoses of patients in the study population.

In conclusion, this study revealed that LNM for Siewert type II/III EGC was mainly associated with macroscopically elevated lesions and lymphovascular invasion; the long-term survival of patients with these cancer types was favorable. Further large-scale prospective randomized studies are required to establish the clinical significance and prognosis of EGJ adenocarcinomas with LNM.

Authors' Contribution

Conceptualization: Sung Eun Kim. Data curation: Min Young Son, Dae Hyeon Cho, Sung Eun Kim. Formal analysis: Min Young Son, Sung Eun Kim. Methodology: Sung Eun Kim. Supervision: Sung Eun Kim, Seun Ja Park, Moo In Park, Won Moon. Writing—original draft: Min Young Son, Dae Hyeon Cho, Sung Eun Kim. Writing—review & editing: Sung Eun Kim, Jae Hyun Kim, Jung Wook Lee, Kyoungwon Jung. Approval of final manuscript: all authors.

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