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Original Article

Worse Survival of Patients With T1 Stage II Gastric Cancer Following Radical Gastrectomy

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ABSTRACT

Purpose: Lymph node (LN) metastasis is a crucial factor in the prognosis of patients with gastric cancer (GC) and is known to occur more frequently in cases with an advanced T stage. This study aimed to analyze the survival data of patients with advanced LN metastasis in T1 GC.
Materials and Methods: From January 2008 to June 2018, 677 patients with pathological stage II GC who underwent radical gastrectomy were divided into an early GC group (EG: T1N2 and T1N3a, n=103) and an advanced GC (AGC) group (AG: T2N1, T2N2, T3N0, T3N1, and T4aN0, n=574). Short- and long-term survival rates were compared between the 2 groups.
Results: A total of 80.6% (n=83) of the patients in the EG group and 52.8% (n=303) in the AG group had stage IIA AGC. The extent of LN dissection, number of retrieved LNs, and short-term morbidity and mortality rates did not differ between the 2 groups. The 5-year relapse-free survival (RFS) of all patients was 87.8% and the overall survival was 84.0%. RFS was lower in the EG group than in the AG group (82.2% vs. 88.7%, P=0.047). This difference was more pronounced among patients with stage IIA (82.4% vs. 92.9%, P=0.003).
Conclusions: T1 GC with multiple LN metastases seems to have a worse prognosis compared to tumors with higher T-stages at the same level. Adjuvant chemotherapy is highly recommended for these patients, and future staging systems may require upstaging T1N2-stage tumors.

Keywords: Stomach neoplasms; Lymphatic metastasis; Lymph nodes

INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies and a major cause of cancer-related deaths worldwide [1]. In Korea, due to a nationwide screening program for GC, the detection rate of early GC (EGC) has increased [2,3]. While endoscopic resection has been accepted as the optional treatment for EGC without the risk of lymph node (LN) metastasis, gastrectomy with adequate perigastric LN dissection is the standard treatment option for EGC [4-6].

The prognosis of patients with EGC is generally better than that of patients with advanced GC (AGC). However, according to the classification outlined in the American Joint Committee on Cancer (AJCC) 8th edition [7], patients with T1N2 and T1N3 are categorized as stages IIA

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and IIB, respectively. Considering that the 5-year survival rate for patients with stage II EGC is approximately 70%–88%, even after undergoing radical gastrectomy, it is expected that patients with stage II EGC exhibit a lower survival rate than those with stage I EGC [8-10]. LN metastasis is a crucial step in the progression of GC and is one of the most significant factors affecting the prognosis [11,12]. Patients with T1N2 and T1N3 disease develop LN metastasis at an early stage of tumor progression. Therefore, their clinical postoperative course may differ from that of patients with AGC who exhibit minimal LN metastasis. Studies have evidenced that due to its distinct clinical course compared to AGC, node-positive EGC is inadequately addressed by the AJCC classification system in predicting patient prognosis [13-16]. Furthermore, various guidelines recommend adjuvant chemotherapy after radical gastrectomy in patients with stage II to improve patient prognosis [5,17,18]. However, there are no reports on how patients' clinical courses differ based on the extent of LN metastasis in stage II GC or any treatment guidelines for patients with EGC with extensive LN metastasis.

This study aimed to analyze the survival data of patients with T1N2 and T1N3a, comparing their outcomes with those of patients with stage II AGC to gain insights and offer better treatment plans for these patients.

MATERIALS AND METHODS

Patients

From January 2008 to June 2018, a total of 5,128 patients with pathologically confirmed GC underwent gastrectomy at 2 affiliated hospitals of the Catholic Medical Center, Korea. Among them, 747 (14.6%) received a postoperative pathological stage II diagnosis. We excluded 58 patients with neoplasms in other organs, 8 patients who underwent neoadjuvant chemotherapy, and 4 whose pathologic or surgical records were not adequate for analysis. Ultimately, 677 patients were enrolled, with T1N2 and T1N3a cases classified in the EGC group (EG, n=103) and T2N1, T2N2, T3N0, T3N1, and T4aN0 cases grouped in the AGC group (AG, n=574, **Table 1**). We compared clinicohistological data, operative parameters, adjuvant chemotherapy data, and long-term survival outcomes between these 2 groups. Postoperative morbidity was defined as complications rated grade 2 or higher according to the Clavien–Dindo grading system [19]. This study was approved by the Institutional Review Board of the Catholic University of Korea College of Medicine (XC22RIDI0025), and the requirement for informed consent was waived because of its retrospective and observational nature.

Surgical treatment and adjuvant chemotherapy

Four surgeons operated the enrolled patients from 2008 to 2018, and all had experience with more than 500 gastrectomies at the time of the operation. Decisions regarding the

Table 1. Patient grouping (EG vs. AG)

Group	N0	N1	N2	N3a
EG (n=103)				
T1			IIA: 83 (80.6%)	IIB: 20 (19.4%)
AG (n=574)				
T2		IIA: 96 (16.7%)	IIB: 79 (13.7%)	
T3	IIA: 207 (36.1%)	IIB: 109 (19.0%)		
T4a	IIB: 83 (14.5%)			

Staging was performed according to the staging system outlined in the American Joint Committee on Cancer 8th edition [7].
EG = early gastric cancer group; AG = advanced gastric cancer group.

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extent of resection and lymphadenectomy complied with the treatment guidelines of the Japanese Gastric Cancer Association [5]. After postoperative recovery, the patients with medical conditions suitable for chemotherapy received adjuvant chemotherapy. Patients with poor performance status or those who refused to receive chemotherapy were excluded from chemotherapy treatment. The surgical oncologists selected the therapeutic regimen according to each patient's medical condition.

Statistical analysis

The data are expressed as medians and interquartile ranges (25th–75th percentiles) for nonparametric continuous variables, as the means ± standard deviations for parametric continuous variables, and as frequencies with percentages for nominal variables. The chi-square test or Fisher's exact test was used for nominal variables. The Mann–Whitney U test was applied for nonparametric variables, and Student's t-test was applied for parametric and continuous variables. Significance was determined using a 2-tailed P-value <0.05. Survival curves were estimated using the Kaplan—Meier method. Variables found to be significant in previous studies were used for univariate analysis, and those found to be significant (P<0.10) in univariate analysis were included in the multivariate Cox proportional hazard regression model to identify prognostic variables related to relapse-free survival (RFS) and overall survival (OS). Statistical analyses were performed using PASW Statistics for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) and R 3.4.2 (R Core Team [2017], Vienna, Austria).

RESULTS

Clinicopathologic characteristics of the 2 groups

According to the pathological stage, 80.6% of patients in the EG were in stage IIA and 19.4% in stage IIB. In the AG, 52.8% of patients were in stage IIA and 47.2% in stage IIB (**Tables 1** and **2**). Patients in the EG were younger than those in the AG and more patients in the AG underwent minimally invasive gastrectomy and total gastrectomy than those in the EG. Tumor size, histological characteristics (including Lauren classification and differentiation), and the number of retrieved LNs were not significantly different between the 2 groups. Lymphovascular invasion was observed more frequently in the EG. The postoperative morbidity and mortality rates were not significantly different between the 2 groups.

Survival outcome and adjuvant chemotherapy

The median follow-up period was 58 months. The 5-year RFS of the enrolled patients was 87.8%. The RFS rates of patients with stage IIA and IIB were 90.8% and 83.9%, respectively. The 5-year OS rate for the enrolled patients was 84.0%. The OS rates of patients with stage IIA and IIB were 86.4% and 80.7%, respectively. **Fig. 1A** illustrates the Kaplan-Meier survival curves of the 5-year RFS for the 2 groups. The 5-year RFS rates were 82.2% and 87.9% in EG and AG, respectively (P=0.047). **Fig. 1B** shows the survival curves of 5-year OS for the 2 groups. The 5-year OS rates were 80.4% and 84.6% in EG and AG, respectively (P=0.406). In stage IIA patients, the 5-year RFS rates were 82.4% and 92.9% in the EG and AG, respectively (P=0.003; **Fig. 2A**). In patients with stage IIB disease, the 5-year RFS rates were 81.5% and 83.9% in the EG and AG groups, respectively (P=0.837, **Fig. 2B**).

Of the total of patients, 70.6% underwent adjuvant chemotherapy, and the proportion of patients who underwent chemotherapy was not significantly different between the 2 groups (68.9% vs. 71.1%, P=0.746, **Table 3**). TS-1 was the most frequently prescribed

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Table 2. Clinicopathologic characteristics

Characteristics	EG (n=103)	AG (n=574)	P-value
Age (yr)	58.0 (50.5–68.0)	63.0 (53.0–72.0)	0.014
Sex			0.271
Male	65 (63.1)	397 (69.2)	
Female	38 (36.9)	177 (30.8)	
BMI (kg/m^2)	23.8 (21.9–26.1)	23.5 (21.5–25.7)	0.334
Surgical approach			0.013
Open	58 (56.3)	244 (42.5)	
Minimally invasive	45 (43.7)	330 (57.5)	
Extent of resection			0.001
Subtotal	89 (86.4)	399 (69.5)	
Total	14 (13.6)	175 (30.5)	
Lymph node dissection			0.180
D1+	30 (29.1)	129 (22.5)	
D2	73 (70.9)	445 (77.5)	
Tumor size (cm)	4.2 (2.6–5.7)	4.3 (3.2–6.0)	0.161
Stage			<0.001
IIA	83 (80.6)	303 (52.8)	
IIB	20 (19.4)	271 (47.2)	
Histologic type			0.619
Differentiated	46 (44.7)	238 (41.5)	
Undifferentiated	57 (55.3)	336 (58.5)	
Lauren classification			0.628
Intestinal type	39 (37.9)	245 (42.7)	
Diffuse type	30 (29.1)	161 (28.0)	
Mixed type	25 (24.2)	133 (23.2)	
Indeterminate	9 (8.8)	35 (6.1)	
Lymphovascular invasion			<0.001
Absent	17 (16.5)	221 (38.5)	
Present	86 (83.5)	353 (61.5)	
Retrieved lymph node	39.0 (29.0–48.5)	40.0 (30.0–51.0)	0.267
30-Day morbidity	24 (23.3)	107 (18.6)	0.334
30-Day mortality	0	4 (0.7)	0.880

Values are presented as median (interquartile range) or number (%).
EG = early gastric cancer; AG = advanced gastric cancer; BMI = body mass index.

chemotherapy drug, followed by capecitabine and oxaliplatin (CAPOX). The proportion of each chemotherapeutic agent was not significantly different between the 2 groups, and no discrepancy was found regardless of the stage (IIA vs. IIB). During the follow-up period, 74 (10.9%) patients experienced tumor recurrence (**Table 3**). Recurrence was more frequently observed in the EG than in the AG (15.5% vs. 10.1%, P=0.010). Lymphatic spread and hematogenous metastasis were the 2 most frequent metastasis patterns in the EG, whereas the peritoneal seeding pattern was dominant in the AG. In 19 patients with recurrence through lymphatic spread, 17 (89.5%) evidenced recurrence at distant LNs, such as those in the para-aortic or retropancreatic area, whereas in the other 2 patients in the AG, each one each presented lymphatic recurrence in the hepatoduodenal area and in the LNs around the celiac axis. The treatment after recurrence for each patient is described in **Table 3**.

During the follow-up period, 102 patients died (18 in the EG and 84 in the AG, P=0.553). In the EG, 11 (61.1%) patients died from GC-related causes, and in the AG, 37 (44.0%) died from GC-related causes; there was no significant difference between the 2 groups (P=0.291).

Because there is no evidence for categorizing patients undergoing adjuvant chemotherapy into the T3N0 and T1N2 categories, we conducted a subgroup analysis for these patients [20]. Patients who underwent chemotherapy were younger than those who did not in both

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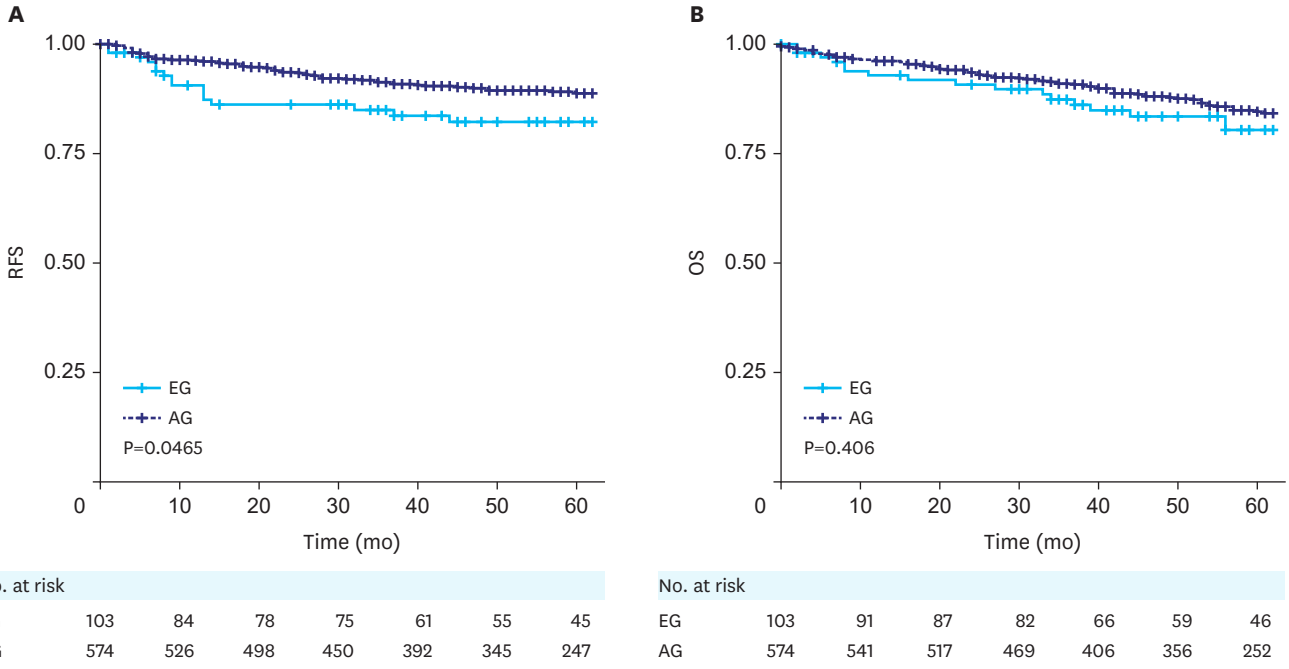
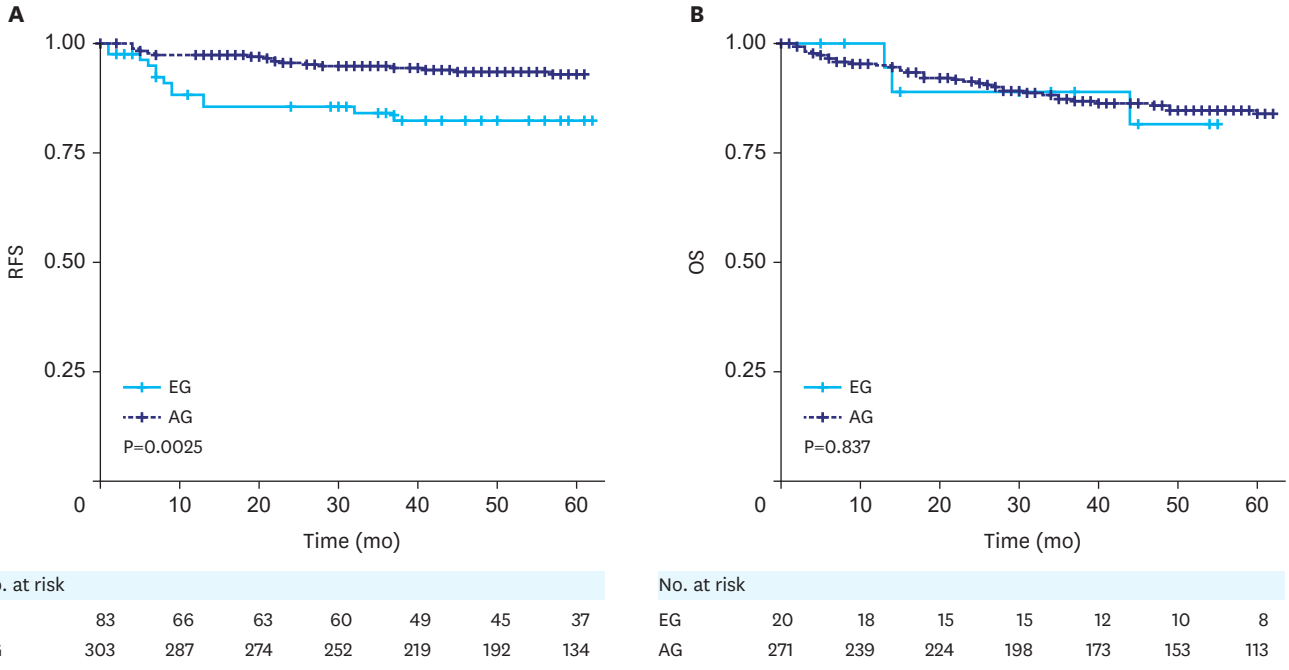


No. at risk							
EG	103	84	78	75	61	55	45
AG	574	526	498	450	392	345	247

No. at risk							
EG	103	91	87	82	66	59	46
AG	574	541	517	469	406	356	252

Fig. 1. Five-year RFS (A) and OS (B) for all enrolled patients.
RFS = relapse-free survival; OS = overall survival; EG = early gastric cancer group; AG = advanced gastric cancer group.



No. at risk							
EG	83	66	63	60	49	45	37
AG	303	287	274	252	219	192	134

No. at risk							
EG	20	18	15	15	12	10	8
AG	271	239	224	198	173	153	113

Fig. 2. Five-year relapse-free survival of patients with stage IIA (A) and stage IIB (B).
RFS = relapse-free survival; OS = overall survival; EG = early gastric cancer group; AG = advanced gastric cancer group.

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Table 3. Adjuvant chemotherapy and 5-year recurrence pattern

Variables	EG (n=103)	AG (n=574)	P-value
Adjuvant chemotherapy			0.746
None or incomplete	32 (31.1)	166 (28.9)	
Done	71 (68.9)	408 (71.1)	0.342
TS-1(±) cisplatin	51 (49.5)	328 (57.1)	
CAPOX	7 (6.8)	32 (5.6)	
FOLFOX	2 (1.9)	3 (0.5)	
Other*	11 (10.7)	45 (7.8)	
Recurrence			0.010
None	87 (84.5)	516 (89.9)	
Yes	16 (15.5)	58 (10.1)	
Peritoneal seeding	1 (1.0)	25 (4.4)	
Hematogenous spread	6 (5.8)	15 (2.6)	
Lymphatic spread	7 (6.8)	12 (2.1)	
Local recurrence	2 (1.9)	6 (1.0)	
Treatment after recurrence			
Surgical therapy	0	4 (0.7)	
Chemotherapy	10 (9.7)	26 (4.5)	
Radiotherapy	1 (1.0)	5 (0.9)	
Conservative care	5 (4.9)	23 (4.0)	

Values are presented as number (%).
EG = early gastric cancer; AG = advanced gastric cancer; CAPOX = capecitabine plus oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin plus oxaliplatin.
*FOLFIRI, 5'-deoxy-5-fluorouridine, FP, LF, TU (±) cisplatin.

groups (61.0 vs. 68.5 in T3N0 and 57.1 vs. 63.6 in T1N2, P<0.001, not shown). In the T3N0 group, there was no difference in OS or RFS between patients who did and did not receive chemotherapy (**Fig. 3A and B**). However, in the T1N2 group, the 5-year OS rates were 60.3% for patients who did not receive chemotherapy and 93.5% for patients who did (P<0.001; **Fig. 3C**). The 5-year RFS rates were 67.1% for patients who did not receive chemotherapy and 89.3% for patients who did (P=0.006).

Cox proportional hazards regression analysis for survival

Univariate Cox proportional hazards regression analysis evidenced that EG, age >70 years, stage IIB disease, and total gastrectomy were significant factors (P<0.10) for RFS (**Table 4**). The T and N stages were excluded from the analysis because they were already utilized in the patient grouping. In the multivariate analysis of RFS, these 4 factors, including EG, were also significant. The hazard ratio of EG for RFS was 2.35. Univariate Cox proportional hazards

Table 4. Cox proportional hazards regression analysis for 5-year recurrence-free survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr ≥70)	2.18 (1.37–3.47)	0.001	2.3 (1.45–3.67)	<0.001
Sex (male)	1.31 (0.82–2.10)	0.260		
Approach (open)	1.15 (0.72–1.84)	0.548		
Total gastrectomy	1.62 (1.01–2.58)	0.046	1.78 (1.11–2.86)	0.017
D2 LND (vs. D1+)	1.08 (0.63–1.86)	0.771		
Lauren classification (diffuse)	1.06 (0.67–1.70)	0.793		
Poorly differentiated	0.96 (0.61–1.53)	0.869		
Adjuvant chemotherapy	0.70 (0.43–1.13)	0.145		
Stage IIB (vs. IIA)	1.64 (1.04–2.59)	0.034	1.81 (1.13–2.91)	0.014
EG (vs. AG)	1.68 (0.96–2.91)	0.068	2.35 (1.31–4.19)	0.003

HR = hazard ratio; CI = confidence interval; LND = lymph node dissection; EG = early gastric cancer group; AG = advanced gastric cancer group.

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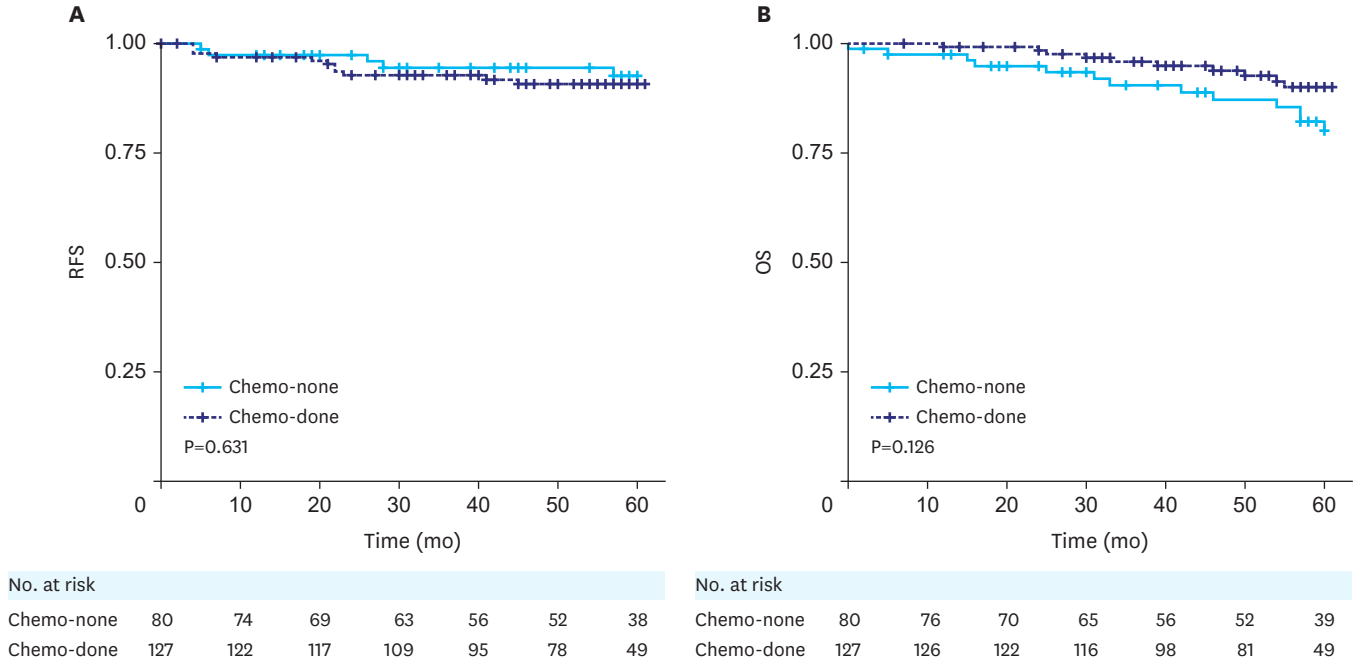

No. at risk							
Chemo-none	80	74	69	63	56	52	38
Chemo-done	127	122	117	109	95	78	49

No. at risk							
Chemo-none	80	76	70	65	56	52	39
Chemo-done	127	126	122	116	98	81	49

No. at risk							
Chemo-none	29	17	15	15	14	14	13
Chemo-done	54	49	48	45	35	31	24

No. at risk							
Chemo-none	29	22	19	19	15	15	13
Chemo-done	54	51	51	46	37	32	24

Fig. 3. Five-year RFS (A) and OS (B) for patients with T3N0 and 5-year RFS (C) and OS (D) for patients with T1N2.
RFS = relapse-free survival; OS = overall survival.

regression analysis for OS showed that age >70 years, stage IIB disease, chemotherapy, LN dissection, and total gastrectomy were significant risk factors (P<0.10) (**Table 5**). In multivariate analysis of OS, age >70 years, stage IIB disease, total gastrectomy, and chemotherapy were identified as significant independent factors.

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Table 5. Cox proportional hazards regression analysis for 5-year overall survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr ≥70)	3.15 (2.13–4.65)	<0.001	2.32 (1.52–3.56)	<0.001
Sex (male)	1.08 (0.72–1.63)	0.706		
Approach (open)	1.00 (0.67–1.49)	0.992		
Total gastrectomy	1.60 (1.07–2.38)	0.022	1.60 (1.07–2.39)	0.021
D2 LND (vs. D1+)	0.69 (0.46–1.04)	0.077	0.82 (0.53–1.25)	0.347
Lauren classification (diffuse)	0.78 (0.53–1.16)	0.218		
Poorly differentiated	0.78 (0.53–1.16)	0.199		
Adjuvant chemotherapy	0.34 (0.23–0.50)	<0.001	0.42 (0.27–0.64)	<0.001
Stage IIB (vs. IIA)	1.76 (1.19–2.61)	0.004	1.88 (1.26–2.79)	0.002
EG (vs. AG)	0.81 (0.48–1.34)	0.407		

HR = hazard ratio; CI = confidence interval; LND = lymph node dissection; EG = early gastric cancer group; AG = advanced gastric cancer group.

DISCUSSION

Despite its retrospective design, this study showed that in stage II GC, T1 tumors with N2 or N3a could have a worse prognosis than T2–4 tumors. Compared to the AG, the EG contained a greater proportion of patients with stage IIA but showed worse survival rate. The survival gap between the 2 groups was significantly wider in patients with stage IIA. In stage II, T1N2 or T1N3a were significant risk factors for tumor recurrence. Even after similar adjuvant chemotherapy profiles, the recurrence patterns differed between the 2 groups. Patients with T1N2 disease showed significant survival differences between those who did and did not receive chemotherapy. To the best of our knowledge, these results have not been previously addressed in the literature. Thus, this study provides multiple points of discussion regarding the diagnosis, surgical treatment, and postoperative treatment of stage II GC.

Adequate LN dissection is essential for GC surgery. For AGC and EGC with suspected LN metastasis, D2 LN dissection is a standard treatment option [5,17,18]. Only for patients with cT1N0, D1+ LN dissection is recommended. In our study, although we strictly followed these recommendations, 29.1% of the patients in the EG and 22.5% of the patients in the AG underwent D1+ LN dissection. Although the proportion of patients who underwent D1+ LN dissection decreased as the T stage advanced, D1+ LN dissection in AGC might have been performed due to preoperative diagnostic underestimation or microscopic tumor overextension, even though the preoperative endoscopic feature was an EGC-like morphology. Considering that discrepancies between the clinical or surgical stage and final pathological stage could exist even for experienced surgeons, extensive LN metastasis may remain a microscopic LN metastasis after “adequate” LN dissection [21]. This assumption may be supported by the finding that lymphatic recurrence was more frequent in the EG than in the AG, according to long-term follow-up data. Additionally, distant metastasis through the hematogenous route was more frequent in the EG, despite a lower T stage. This finding suggests that patients with extensive LN metastasis might be vulnerable to systemic tumor recurrence, and more caution and aggressive adjuvant chemotherapy are needed for these patients, even with a T1 stage.

In far-eastern countries, for patients with stage II and III GC, adjuvant chemotherapy is strongly recommended for survival benefits even after radical gastrectomy with D2 LN dissection [5,17,18]. In a Japanese trial of TS-1 in GC (ACTS-GC), TS-1 showed a clear survival benefit in patients with stage II or III [22]. In the CLASSIC trial conducted in South

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Korea, Taiwan, and China, CAPOX also showed survival benefits in patients with stage II–IIIB disease [23]. In some trials in Korea, Japan, and China, TS-1 plus oxaliplatin (SOX) or cisplatin showed a clinical benefit similar to that of TS-1 monotherapy or the CAPOX regimen for patients with locally AGC; however, most of these trials included patients who received neoadjuvant chemotherapy setting [24-28]. Clinical evidence for the additional survival benefits of CAPOX or SOX over TS-1 in patients with stage II disease has not yet been elucidated. Although a randomized phase III trial (ARTIST-2) showed the superiority of SOX over S-1 monotherapy for stage II or III GC with positive LNs, subgroup analysis did not show clear evidence in the stage II group [29]. In AGC, the change that separates stages II and III is mostly advanced LN metastasis; except for T2N2, all N2 and N3 stages with T2–4 are stage III. In a multicenter trial in Korea, the CAPOX regimen was superiority in terms of 3-year RFS over TS-1 in stage IIIB and IIIC [30]. Similarly, if the survival superiority of CAPOX exists in patients with stage III with advanced LN metastasis, similar results may be observed in patients with stage II and advanced LN metastasis. In the multivariate analysis of OS in our study, adjuvant chemotherapy was identified as a significant protective prognostic factor (**Table 5**). A survival benefit of adjuvant chemotherapy was also identified in the T1N2 group, which to date has not been supported by previous studies (**Fig. 3C and D**) [20]. Further well-designed investigations are required to improve the long-term survival of this population.

In our study, the 5-year RFS of patients with pT1N2 was 82.4% and the 5-year RFS rate of all patients with stage IIB disease was 83.9%. pT1N2 is classified as stage IIA in the AJCC 8th edition [7], but the long-term survival of these patients was not superior to that of patients with stage IIB in our study (P=0.541, not shown). An analysis with a larger population should be performed. If similar results support the findings of our study, upstaging of this population to stage IIB should be carefully considered. In the 8th edition of the AJCC staging manual, T1–3N3b was upstaged from IIB, IIIa, and IIIB to IIIB, IIIB, and IIIC, respectively [7].

The major limitation of this study is its retrospective design. There were discrepancies in the extent of gastrectomy and proportion of patients who underwent minimally invasive surgery. Total gastrectomy and open surgery are usually considered negative prognostic factors for short- and long-term outcomes [31,32]. In our study, the EG included more patients who underwent open gastrectomy and the AG included more patients who underwent total gastrectomy, which was analyzed as a negative prognostic factor for RFS. This result might not conflict with our findings; however, a well-designed study is required. Additionally, during the study period, some patients were enrolled in the KLASS-01 randomized controlled study; therefore, the proportion of patients undergoing open gastrectomy for EGC was relatively large [33]. Moreover, our study did not include information about the preoperative stage, and the possibility of understaging in patients who might have had extensive preoperative distant metastases and showed recurrence after surgery should not be ignored. Finally, the number of patients with T1N3a was relatively small, indicating a limitation in revealing survival discrepancies between T2N2, T3N1, and T4aN0. With a larger number of patients with T1N3a than in our study, the impact of extensive LN metastasis in patients with stage T1 on long-term prognosis should be clarified in the future.

In conclusion, among stage II tumors, T1N2 and T1N3a tumors seem to have worse prognoses than deeper T stage tumors. Adjuvant chemotherapy is highly recommended to manage these tumors, and T1N2 stage tumors may require upstaging in future staging systems.

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