original article

Early and late recurrences in lymph node-negative gastric cancer: a retrospective cohort study

Jian-Wei Sun,[a] Dao-Li Liu,[b] Jia-Xian Chen,[a] Li-Zhen Lin,[c] Lv-Ping Zhuang,[d] Xian-Hai Hou[a]

From the [a]Department of Surgery, Qingyang's People's Hospital, Qingyan, China; [b]Department of Gastrointestinal Surgery, Anqing First People's Hospital of Anhui Medical University, Anqing, China; [c]Graduate School, Fujian Medical University, Fuzhou, China; [d]Department of Neurology, Fujian Medical University Union Hospital, Fuzhou, China

Correspondence: Prof. Xian-Hai Hou · Department of Surgery, Qingyang's People's Hospital, No. 608 South Road Qingyang Gansu Province 745000 China · 15294427679@163.com · ORCID: https://orcid.org/0000-0002-1005-1958

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BACKGROUND: Predictors of recurrence in patients with lymph node-negative gastric cancer (GC) who have undergone curative resection have been widely investigated, but not the effects of predictors on timing of recurrence.

OBJECTIVE: Determine the factors associated with early and late recurrence in patients with node-negative GC.

DESIGN: Retrospective cohort.

SETTING: Academic tertiary care center.

PATIENTS AND METHODS: The study included patients with node-negative GC after curative resection between 2008 and 2018 at two institutions. Early and late recurrences were determined using a minimum *P* value approach to evaluate the optimal cutoff for recurrence-free survival (RFS). A competing risk model and landmark analysis were used to analyze factors associated with early and late recurrences.

MAIN OUTCOME MEASURES: Recurrence-free survival and factors associated with survival.

SAMPLE SIZE: 606.

RESULTS: After a median follow-up of 70 months, 50 (8.3%) patients experienced recurrent disease. The optimal length of RFS for distinguishing between early (n=26) and late recurrence (n=24) was 24 months (*P*=.0013). The median RFS in the early and late recurrence groups was 11 and 32 months, respectively. Diffuse tumors (hazard ratio 3.358, *P*=.014), advanced T stage (HR 8.804, *P*=.003), perineural invasion (HR 10.955, *P*<.001), and anemia (HR 2.351, *P*=.018) were independent predictors of early recurrence. Mixed tumor location (HR 5.586, *P*=.002), advanced T stage (HR 5.066, *P*<.001), lymphovascular invasion (HR 5.902, *P*<.001), and elevated CA19-9 levels (HR 5.227, *P*<.001) were independent predictors of late recurrence. Similar results were obtained in the landmark analysis.

CONCLUSIONS: Individualized therapeutic and follow-up strategies should be considered in future studies because of distinct patterns in predictors of early and late recurrence.

LIMITATIONS: Retrospective design, small sample size.

CONFLICT OF INTEREST: None.

Gastric cancer (GC) is the fifth most frequently diagnosed cancer worldwide and the third leading cause of cancer death.[1] At present, radical gastrectomy with adequate lymphadenectomy remains the cornerstone of treatment for GC.[2] Lymph node status is a well-known prognostic factor for GC recurrence and survival after surgical resection.[3,4] Although lymph node-negative patients show substantially better survival than those with node-positive disease, recurrence is still noted in a subset of node-negative patients. Thus, factors associated with recurrence in patients with node-negative disease have been the focus of current research.[5-8]

In recent decades, cumulative evidence has demonstrated distinctions between early and late recurrence in several cancers, including hepatocellular carcinoma, gastric adenocarcinoma, and pancreatic ductal adenocarcinoma.[9-11] In most patients with GC who experience recurrence, relapse occurs relatively soon after radical resection and usually heralds a worse prognosis than when disease recurrence occurs a long time after surgery.[12-14] Moreover, it has been reported that predictors of early and late recurrence are significantly different in patients with GC after endoscopic submucosal dissection or radical gastrectomy.[9,15,16] For patients with GC, exploring the risk factors of early and late recurrence is of great significance for the selection of adjuvant treatment and subsequent surveillance. However, this topic has not been studied in patients with lymph node-negative GC. We conducted a multicenter retrospective study to identify the risk factors for early and late cancer recurrence in patients who underwent curative surgery.

PATIENTS AND METHODS

Data were selected from a cohort of patients with GC who underwent radical gastrectomy between January 2008 and January 2018 at two institutions in China. The institutional review boards of the participating institutions approved the study. Inclusion criteria were as follows: the presence of primary gastric adenocarcinoma with more than 15 lymph nodes pathologically analyzed after surgery, all results negative for metastases on routine hematoxylin-eosin staining, no preoperative chemotherapy and/or radiotherapy, no combined malignancies, no distant metastasis, complete basic information, and complete survival data. Exclusion criteria were as follows: histology showing a tumor type other than adenocarcinoma, remnant GC, and tumor invading the adjacent structures. Routine clinicopathological data were collected. All surgical procedures, including D2 lymph node dissections, were performed according to the Japanese Gastric Cancer Treatment Guidelines.[17,18] The TNM classification (American Joint Committee on Cancer, 8th edition) was used for tumor staging.[19] Patients with stage II-III GC were routinely recommended to receive six cycles of adjuvant chemotherapy after surgery every 3 weeks. The regimen consisted of an intravenous infusion of oxaliplatin and oral administration of capecitabine (XELOX) or S-1 (SOX). S-1 is a combination of tegafur (prodrug of 5-fluorouracil), 5-chloro-2,4-dihydroxypyridine (dihydropyrimidine dehydrogenase inhibitor); and potassium oxonate (reduces gastrointestinal toxicity).

Definitions

Recurrence was defined as the presence of a biopsy-proven tumor showing adenocarcinoma cells or imaging features highly suspicious of tumor recurrence.[20] Recurrence was categorized by the site involved: locoregional, peritoneal, distant, or multiple.[8,21,22] The presence of recurrent disease in two or more sites was defined as multiple recurrence. Multiple recurrent lesions in the same area (e.g., liver) were not classified as multiple recurrences. Although some patients had multiple recurrence episodes, this study analyzed only the initial recurrence episode, as defined above. The presence of anemia was defined as a hemoglobin level <12.0 g/dL for men and <11.0 g/dL for women. Overall survival (OS) was defined as the time from surgery to death. Disease-specific survival (DSS) was defined as the time interval from surgery to death from GC. Recurrence-free survival (RFS) was measured from the date of curative resection to the date of disease recurrence. Post-recurrence survival (PRS) was defined as the period from the initial recurrence to either death or the last follow-up. When patients were diagnosed with recurrence, systemic chemotherapy or supportive therapy were usually recommended according to the patient's willingness after a discussion with the multidisciplinary team.

Follow-up

All patients received standard postoperative follow-ups, including 3-monthly visits for the first 2 years, 6-monthly reviews from the third to fifth year, and annually thereafter. Most routine follow-up appointments included physical examination, laboratory testing, chest radiography, and abdominopelvic ultrasonography or computed tomography. Annual endoscopy was also recommended. All patients were observed until death or at the final follow-up in June 2020. The median follow-up period was 70 months.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range

(IQR). Categorical variables are presented as frequencies and percentages. Differences between the groups were assessed using the *t* test, Mann-Whitney test, Fisher's exact test, or the χ^2 test, as appropriate. Survival analysis was assessed using Kaplan-Meier survival curves, which were estimated using the Kaplan-Meier method. A log-rank test was used to determine the statistical significance. A minimum ^{P} value approach was used to evaluate the optimal threshold of RFS to divide the patients into early and late recurrence groups based on the duration of PRS.[11,14] We conducted competing risk analyses to identify independent prognostic factors associated with early and late recurrence. When exploring risk factors for early recurrence, the case group comprised patients who experienced early recurrence, while the control group comprised the remaining patients, including those who experienced late recurrence. When exploring risk factors for late recurrence, the case group comprised patients who experienced late recurrence, while the control group comprised those who survived for >24 months and did not experience recurrence. The Fine and Gray competing risk model was used to obtain subhazard ratios (SHRs) and adjusted subhazard ratios (aSHRs).[23,24] Variables with a value of *P*<.05 in the univariate analysis were subsequently included in a multivariate analysis. Statistical analyses were performed using IBM SPSS version.22.0 for Windows (IBM, Armonk, New York, United States) and R software (version 3.6.1; R Foundation for Statistical Computing; *https://www.r-proje ct.org/*). The competing risk model was performed using the R software, and the landmark analysis was performed using SPSS. All tests were two-sided with a significance level of *P*<.05.

RESULTS

The 606 patients with lymph node-negative gastric adenocarcinoma who underwent curative-intent resection included 479 patients from Fujian Medical University Health System (Fuzhou, Fujian Province) and 127 from Qingyang People's Hospital (Qingyang, Gansu Province). The baseline characteristics of the patients are shown in **Table 1**. Of these, 244 patients (40.3%) underwent open gastrectomy and 362 (59.7%) underwent laparoscopic gastrectomy. After a median follow-up of 70 months (IQR, 60-84 months), 50 patients (8.3%) experienced disease recurrence. Compared with pa-

Table 1. Clinicopathological characteristics of patients with and without recurrence..

	Total (n=606)	No recurrence (n=556)	Recurrence (n=50)	*P* value
Age (years), mean (SD)	59.6 (11.4)	59.4 (11.2)	62.1 (12.8)	.108
Gender				
Male	452 (74.6)	414 (74.5)	38 (76.0)	.811
Female	154 (25.4)	142 (25.5)	12 (24.0)	
Smoking				
No	415 (68.5)	381 (68.5)	34 (68.0)	.939
Yes	191 (31.5)	175 (31.5)	16 (32.0)	
Family history				
No	575 (94.9)	527 (94.8)	48 (96.0)	.999
Yes	31 (5.1)	29 (5.2)	2 (4.0)	
Helicobacter pylori infection				
No	264 (43.6)	236 (42.4)	28 (56.0)	.064
Yes	342 (56.4)	320 (57.6)	22 (44.0)	
Lauren classification				
Intestinal	367 (60.6)	349 (62.8)	18 (36.0)	**<.001**
Diffuse	239 (39.4)	207 (37.2)	32 (64.0)	
Surgical approach				
Open	244 (40.3)	226 (40.6)	18 (36.0)	.521
Laparoscopic	362 (59.7)	330 (59.4)	32 (64.0)	

Table 1 (cont). Clinicopathological characteristics of patients with and without recurrence.

	Total (n=606)	No recurrence (n=556)	Recurrence (n=50)	*P* value
Type of gastrectomy				
Total	253 (41.7)	218 (39.2)	35 (70.0)	**<.001**
Subtotal	353 (58.3)	338 (60.8)	15 (30.0)	
Tumor location				
Lower 1/3	291 (48.0)	276 (49.6)	15 (30.0)	
Middle 1/3	126 (20.8)	114 (20.5)	12 (24.0)	**.003**
Upper 1/3	126 (20.8)	115 (20.7)	11 (22.0)	
Mixed	63 (10.4)	51 (9.2)	12 (24.0)	
Pathologic T stage				
T1	332 (54.8)	329 (59.2)	3 (6.0)	
T2	89 (14.7)	83 (14.9)	6 (12.0)	**<.001**
T3	127 (21.0)	99 (17.8)	28 (56.0)	
T4[a]	58 (9.6)	45 (8.1)	13 (26.0)	
Lymph node harvested (median, IQR)	27 (20-36)	27 (20-35)	28 (22-40)	.066
Tumor size (mm), mean (SD)	33.4 (21.1)	32.3 (19.9)	45.5 (29.4)	**<.001**
Lymphovascular invasion				
No	546 (90.1)	509 (91.5)	37 (74.0)	**<.001**
Yes	60 (9.9)	47 (8.5)	13 (26.0)	
Perineural invasion				
No	556 (91.7)	527 (94.8)	29 (58.0)	**<.001**
Yes	50 (8.3)	29 (5.2)	21 (42.0)	
Anemia				
No	488 (80.5)	452 (81.3)	36 (72.0)	.112
Yes	118 (19.5)	104 (18.7)	14 (28.0)	
Carcinoembryonic antigen (ng/mL)				
<5.0	547 (90.3)	504 (90.6)	43 (86.0)	.288
≥5.0	59 (9.7)	52 (9.4)	7 (14.0)	
CA19-9 (U/mL)				
<37.0	577 (95.2)	533 (95.9)	44 (88.0)	**.013**
≥37.0	29 (4.8)	23 (4.1)	6 (12.0)	
Postoperative complication				
No	464 (72.0)	428 (77.0)	36 (72.0)	.426
Yes	142 (23.4)	128 (23.0)	14 (28.0)	
Adjuvant chemotherapy				
No	436 (71.9)	414 (74.5)	22 (44.0)	**<.001**
Yes	170 (28.1)	142 (25.5)	28 (56.0)	

Data are number (%) unless otherwise noted. CA199: Carbohydrate antigen 19-9

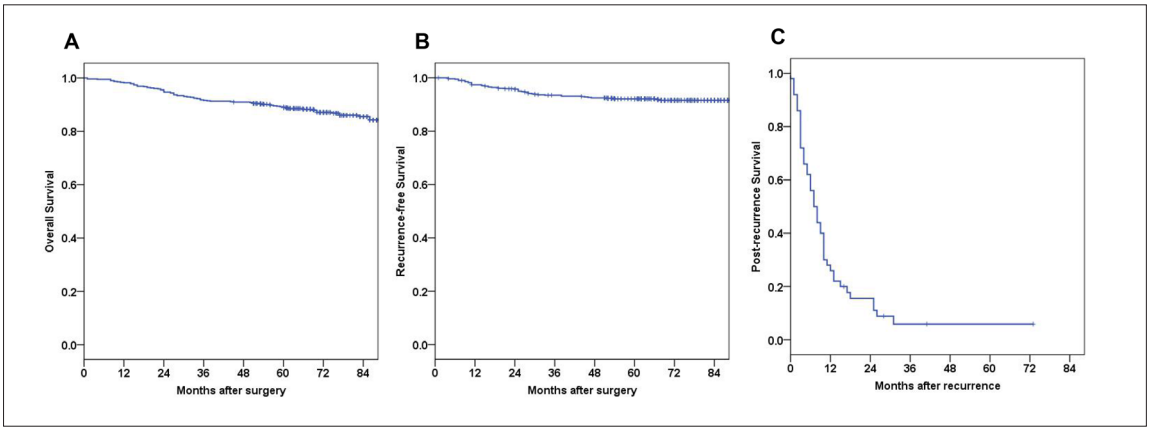

Figure 1. Kaplan-Meier curves for overall survival (A), recurrence-free survival (B), and post-recurrence survival (PRS) (C) of the entire cohort (n=606).

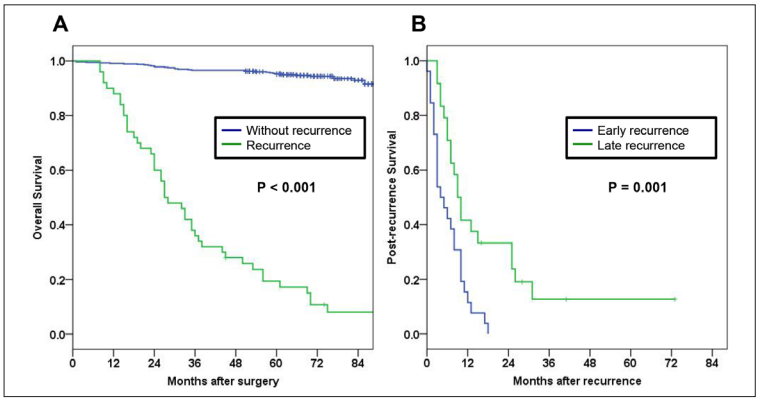

Figure 2. Comparison of overall survival for patients with or without recurrence (A) (n=606); post-recurrence survival (PRS) for patients with early or late recurrence (B) (n=50).

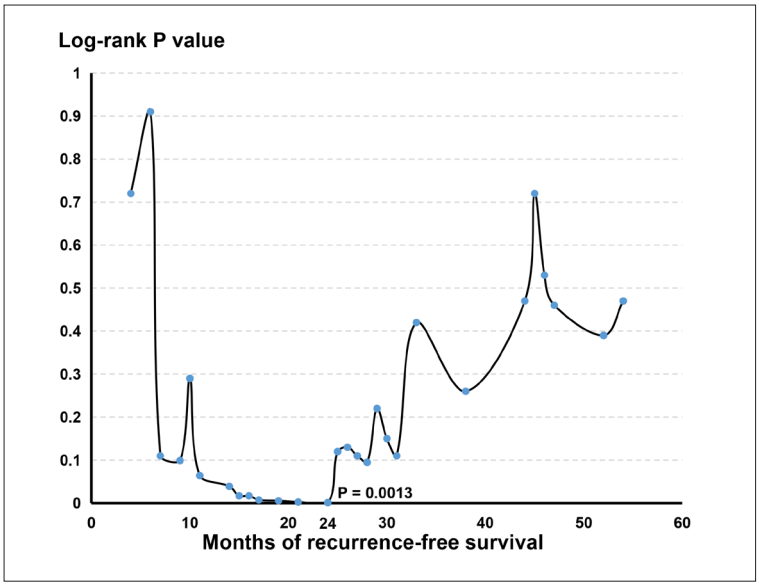

Figure 3. Different cut-off thresholds, with the corresponding *P* values, showing that the optimal threshold for defining early and late recurrence based on the difference in post-recurrence survival (PRS) is 24 months.

tients who did not experience recurrence, patients who experienced recurrence were more likely to have locally more advanced diseases, such as advanced pathologic T stage, lymphovascular invasion, and larger tumor size (**Table 1**). The two groups did not differ with respect to sex, age, or the number of lymph nodes harvested.

Overall and recurrence-free survival

Survival curves for the whole cohort are shown in **Figure 1**. Overall survival (OS) rates were 98.2% at 1 year, 91.6% at 3 years, and 89.1% at 5 years. The 1-year, 3-year, and 5-year DSS rates were 99.0% at 1 year, 94.7% at 3 years, and 93.4% at 5 years. Of the 50 patients who experienced recurrence, the median time to recurrence was 23 months (IQR 11–32 months), with 32% recurrence occurring at 1 year, 52% at 2 years, 78% at 3 years, and 94% at 5 years. The median PRS was only 7.5 months (IQR 3–13 months). Moreover, 74% of the patients died within 1 year. The 5-year OS for patients who experienced recurrence was significantly lower than that for patients who did not have a recurrence (8.0% vs. 96.2%; *P*<.001; **Figure 2A**).

Defining early and late recurrence

The optimal length of RFS to distinguish between early and late recurrence based on the subsequent PRS was 24 months (*P*=.0013, **Figure 3**).The median RFS in the early (<24 months) and late (≥24 months) recurrence groups was 11 months (IQR 9–16 months) and 32 months (IQR 27–47 months), respectively. The median PRS of patients who experienced late recurrence was significantly longer than that of patients with early recurrence (9.5 vs. 4.5 months, *P*=.001, **Figure 2B**). Multivariate analysis showed that late recurrence (HR 0.390, 95% CI 0.182–0.834, *P*<.001) was independently associated with a better PRS in patients who experienced recurrence (**Table 2**).

Table 2. Univariate and multivariate analyses for overall survival after recurrence.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (years)	1.001 (0.979-1.023)	.957		
Gender				
Male	Reference	.338		
Female	1.387 (0.710-2.709)			
Lauren classification				
Intestinal	Reference	.038	Reference	.383
Diffuse	1.941 (1.038-3.630)		1.364 (0.679-2.739)	
Tumor location				
Lower 1/3	Reference	.843		
Middle 1/3	0.747 (0.330-1.691)			
Upper 1/3	0.890 (0.399-1.985)			
Mixed	0.725 (0.326-1.612)			
Pathologic T stage				
T1-2	Reference	.077		
T3-4	2.105 (0.923-4.800)			
Tumor size, mm				
<40	Reference	.085		
≥40	1.692 (0.930-3.081)			
Lymphovascular invasion				
No	Reference	.336		
Yes	0.708 (0.350-1.431)			
Perineural invasion				
No	Reference	.002	Reference	.261
Yes	2.784 (1.460-5.309)		1.531 (0.729-3.218)	
Postoperative complication				
No	Reference	.977		
Yes	1.010 (0.522-1.955)			
Adjuvant chemotherapy				
No	Reference	.284		
Yes	0.726 (0.404-1.304)			
Timing of recurrence, months				
<24	Reference	.003	Reference	**.015**
≥24	0.381 (0.202-0.719)		0.390 (0.182-0.834)	
Anti-tumor treatment after recurrence				
No	Reference	.023	Reference	**.026**
Yes	0.496 (0.271-0.906)		0.456 (0.228-0.910)	

Factors associated with early and late recurrence

Compared with the late recurrence group, the early recurrence group had more diffuse tumors and more perineural invasion (**Table 3**) (*P*=.048 and *P*<.001, respectively). We performed a competing risk model to identify the risk factors associated with early and late recurrences. In the univariate analysis, Lauren classification, T stage, perineural invasion, anemia, and adjuvant chemotherapy were significantly associated with early recurrence (*P*<.05, **Table 4**). In the multivariate analysis, diffuse tumors (HR 3.358, *P*=.014), advanced T stage (HR 8.804, *P*=.003), perineural invasion (HR 10.955, *P*<.001), and anemia (HR 2.351, *P*=.018) were independent predictors of early recurrence. In the univariate analysis, tumor location, T stage, tumor size, lymphovascular invasion, and CA19-9 levels were associated with late recurrence (*P*<.05, **Table 5**). Multivariate analysis showed that mixed tumor location (HR 5.586, *P*=.002), advanced T stage (HR 5.066, *P*<.001), lymphovascular invasion (HR 5.902, *P*<.001), and elevated CA19-9 levels (HR 5.227, *P*<.001) were independent predictors for late recurrence. Patterns of recurrence were similar between the early and late recurrence groups (*P*<.05; **Figure 4**).

Landmark analysis

In the landmark analysis (**Figure 5**), T3-4 disease and perineural invasion were closely associated with disease recurrence in both early (*P*<.001) and late (*P*=.017) periods. Diffuse tumors increased the risk of recurrence in the early period (*P*<.001) but not in the late period (*P*=.205). Moreover, non-lower-third tumors, lymphovascular invasion, and elevated CA19-9 levels did not increase the risk of early recurrence (*P*>.05), but did so for late recurrence (*P*<.001, *P*=.004, and *P*<.001, respectively).

DISCUSSION

In this study, distinct patterns of predictors for early and late recurrence in patients with lymph node-negative GC were demonstrated. Our study showed that patients with node-negative disease had a favorable

Table 3. Clinicopathological characteristics by early and late recurrence.

Characteristic	Early recurrence (n=26)	Late recurrence (n=24)	*P* value
Age (years), mean (SD)	60.2 (12.7)	64.2 (12.9)	.274
Gender			
Male	19 (73.1)	19 (79.2)	.614
Female	7 (26.9)	5 (20.8)	
Smoking			
No	19 (73.1)	15 (62.5)	.423
Yes	7 (26.9)	9 (37.5)	
Family history			
No	25 (96.2)	23 (95.8)	1.000
Yes	1 (3.8)	1 (4.2)	
Helicobacter pylori infection			
No	14 (53.8)	14 (58.3)	.749
Yes	12 (46.2)	10 (41.7)	
Lauren classification			
Intestinal	6 (23.1)	12 (50.0)	**.048**
Diffuse	20 (76.9)	12 (50.0)	
Surgical approach			
Open	7 (26.9)	11 (45.8)	.164
Laparoscopic	19 (73.1)	13 (54.2)	
Type of gastrectomy			
Total	17 (65.4)	18 (75.0)	.459
Subtotal	9 (34.6)	6 (25.0)	

Table 3 (cont.). Clinicopathological characteristics by early and late recurrence.

Characteristic	Early recurrence (n=26)	Late recurrence (n=24)	*P* value
Tumor location			
Lower 1/3	10 (38.5)	5 (20.8)	
Middle 1/3	5 (19.2)	7 (29.2)	.503
Upper 1/3	6 (23.1)	5 (20.8)	
Mixed	5 (19.2)	7 (29.2)	
Pathologic T stage			
T1-2	3 (11.5)	6 (25.0)	.281
T3-4	23 (88.5)	18 (75.0)	
Lymph node harvested, median (IQR)	27 (22-44)	28 (23-43)	.716
Tumor (mm), mean (SD)	46.7 (34.2)	44.2 (23.9)	.762
Lymphovascular invasion			
No	23 (88.5)	14 (58.3)	**.024**
Yes	3 (11.5)	10 (41.7)	
Perineural invasion			
No	9 (34.6)	20 (83.3)	**<.001**
Yes	17 (65.4)	4 (16.7)	
Anemia			
No	15 (57.7)	21 (87.5)	**.028**
Yes	11 (42.3)	3 (12.5)	
Carcinoembryonic antigen (ng/mL)			
<5.0	21 (80.8)	22 (91.7)	.420
≥5.0	5 (19.2)	2 (8.3)	
CA19-9 (U/mL)			
<37.0	25 (96.2)	19 (79.2)	.093
≥37.0	1 (3.8)	5 (20.8)	
Postoperative complication			
No	20 (76.9)	16 (66.7)	.420
Yes	6 (23.1)	8 (33.3)	
Adjuvant chemotherapy			
No	11 (42.3)	11 (45.8)	.802
Yes	15 (57.7)	13 (54.2)	
Anti-tumor treatment after recurrence			
No	10 (38.5)	10 (41.7)	.817
Yes	16 (61.5)	14 (58.3)	

Data are number (%) unless otherwise noted. CA199: carbohydrate antigen 19-9.

Table 4. Competing risk model of risk factors for early recurrence (n=26).

Variables	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P* value	aSHR (95% CI)	*P* value
Age (years)	1.017 (0.978-1.058)	.978		
Gender				
Male	Reference	.334		
Female	0.625 (0.241-1.621)			
Smoking				
No	Reference	.610		
Yes	0.799 (0.336-1.901)			
Helicobacter pylori infection				
No	Reference	.290		
Yes	0.660 (0.306-1.424)			
Lauren classification				
Intestinal	Reference	.002	Reference	**.010**
Diffuse	4.419 (1.739-11.226)		3.710 (1.365-10.080)	
Tumor location				
Lower 1/3	Reference			
Middle 1/3	1.520 (0.505-4.580)	.457		
Upper 1/3	1.666 (0.582-4.769)	.341		
Mixed	2.137 (0.671-6.804)	.199		
Pathologic T stage				
T1-2	Reference	<.001	Reference	**.009**
T3-4	23.679 (6.238-89.883)		7.008 (1.627-30.181)	
Tumor size (mm)				
<40	Reference	.147		
≥40	1.816 (0.811-4.068)			
Lymphovascular invasion				
No	Reference	.502		
Yes	1.516 (0.450-5.107)			
Perineural invasion				
No	Reference	<.001	Reference	**<.001**
Yes	27.955 (11.859-65.898)		12.404 (4.870-31.593)	
Anemia				
No	Reference	.004	Reference	**.018**
Yes	3.158 (1.453-6.863)		2.351 (1.159-4.771)	
Carcinoembryonic antigen (ng/mL)				
<5.0	Reference	.057		
≥5.0	2.600 (0.966-6.999)			

Table 4 (cont.). Competing risk model of risk factors for early recurrence (n=26).

Variables	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P* value	aSHR (95% CI)	*P* value
CA19-9 (U/mL)				
<37.0	Reference	.907		
≥37.0	0.888 (0.120-6.560)			
Postoperative complication				
No	Reference	.950		
Yes	0.972 (0.393-2.416)			
Adjuvant chemotherapy				
No	Reference	<.001	Reference	.082
Yes	4.079 (1.788-9.306)		0.480 (0.210-1.098)	

CA199: Carbohydrate antigen 19-9, SHR: subhazard ratios, aSHR, adjusted subhazard ratio.

Table 5. Competing risk model of risk factors for late recurrence (n=24).

Variables	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P* value	aSHR (95% CI)	*P* value
Age (years)	1.072 (0.981-1.172)	.126		
Gender				
Male	Reference	.898		
Female	0.937 (0.343-2.556)			
Smoking				
No	Reference	.530		
Yes	1.301 (0.569-2.975)			
Helicobacter pylori infection				
No	Reference	.140		
Yes	0.545 (0.243-1.223)			
Lauren classification				
Intestinal	Reference	.111		
Diffuse	1.967 (0.855-4.522)			
Tumor location				
Lower 1/3	Reference		Reference	
Middle 1/3	4.780 (1.439-15.875)	.457	3.703 (1.250-10.968)	**.018**
Upper 1/3	3.436 (0.934-12.637)	.063	1.938 (0.516-6.610)	.290
Mixed	9.971 (2.908-34.185)	<.001	5.586 (1.866-16.709)	**.002**
Pathologic T stage				**<.001**
T1-2	Reference	<.001	Reference	
T3-4	9.840 (3.652-26.515)		5.066 (2.014-12.752)	

Table 5 (cont.). Competing risk model of risk factors for late recurrence (n=24).

Variables	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P* value	aSHR (95% CI)	*P* value
Tumor size, mm				
<40	Reference	.049	Reference	.971
≥40	2.327 (1.003-5.398)		0.984 (0.407-2.376)	
Lymphovascular invasion				
No	Reference	<.001	Reference	**<.001**
Yes	6.166 (2.664-12.275)		5.902 (2.537-13.735)	
Perineural invasion				
No	Reference	.011	Reference	.790
Yes	4.556 (1.417-14.644)		0.863 (0.296-2.510)	
Anemia				
No	Reference	.490		
Yes	0.653 (0.195-2.178)			
CEA (ng/mL)				
<5.0	Reference	.930		
≥5.0	0.937 (0.219-4.001)			
CA19-9 (U/mL)				
<37.0	Reference	<.001	Reference	**<.001**
≥37.0	6.263 (2.290-17.131)		5.227 (2.055-13.288)	
Postoperative complication				
No	Reference	.170		
Yes	1.793 (0.774-4.157)			
Adjuvant chemotherapy				
No	Reference	.405		
Yes	0.629 (0.212-1.871)			

Abbreviations: CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; SHRs, subhazard ratios; aSHRs, adjusted subhazard ratios.

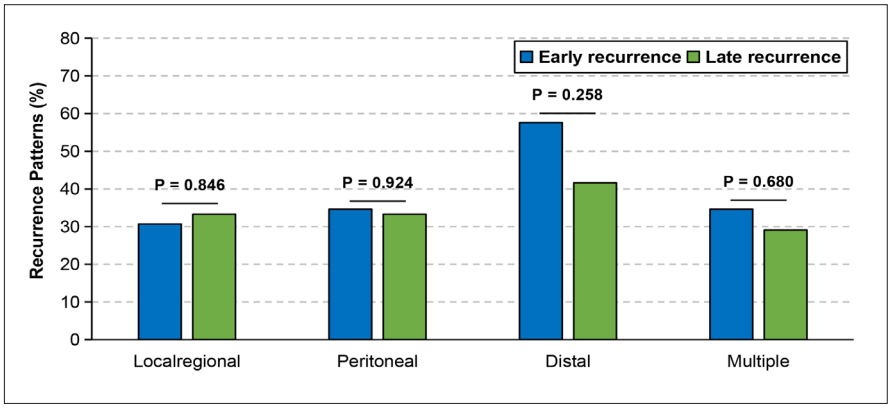

Figure 4. Recurrence patterns in patients with early and late recurrence.

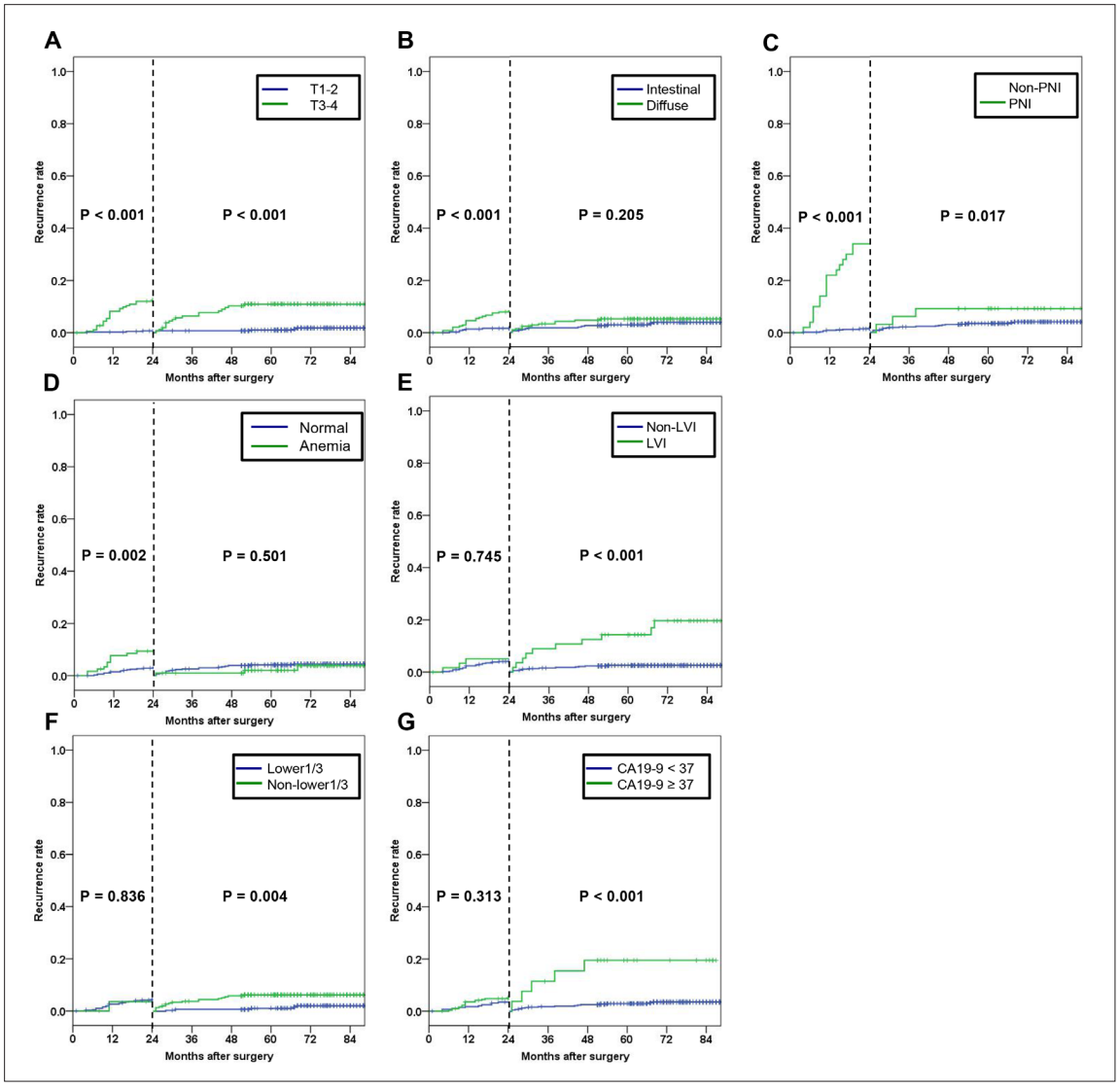

Figure 5. Kaplan-Meier estimates of survival before and after the landmark time (24 months) according to pathologic T stage (A), Lauren classification (B), perineural invasion (PNI) (C), anemia (D), lymphovascular invasion (LVI) (E), tumor location (F), and CA19-9 level (G).

prognosis, with 5-year OS and RFS rates of 89.1% and 92.2%, respectively. To differentiate between early and late recurrence, a recurrence-free interval of 24 months was defined as the optimal threshold based on PRS. Multivariate analyses revealed that the factors associated with late recurrence were quite different from those associated with early recurrence. Diffuse tumors, advanced T stage, perineural invasion, and anemia were independent predictive factors for early recurrence. In contrast, mixed tumors, advanced T stage, lymphovascular invasion, and elevated CA19-9 levels were independent predictive factors for late recurrence.

Lymph node metastasis was the strongest prognostic factor for GC after R0 resection. Compared with node-positive GC, node-negative GC has less aggressive biological features and a better prognosis.[25] Despite this, a small proportion of patients with node-negative disease will experience recurrence and disease-specific death. Thus, identifying prognostic indicators for recurrence has been the focus of several studies in node-negative GC.[5, 26, 27] Among these studies, the depth of tumor invasion was the most important predictor of survival in patients with node-negative GC, which is consistent with our study results. This finding can be explained by the aggressive biological behavior of the disease in patients with advanced T stage.[28,29] In

contrast, the number of metastatic lymph nodes was the most significant factor associated with the prognosis of patients with node-positive GC.[30,31] Moreover, in a retrospective study of 317 patients with node-negative GC from 7 US centers, competing risk regression was used to determine factors associated with time to recurrence.[5] The results suggested that decreased time to recurrence, namely early recurrence, was characterized by T-stage III or higher. Unlike this study, our study demonstrated that T stage was the most important predictor of both early and late recurrence. Thus, patients with advanced T stage were always at a high risk of recurrence, irrespective of time after surgery.

We also found that diffuse histology, tumor location, lymphovascular invasion, perineural invasion, and anemia were significant risk factors for disease recurrence. Based on existing reports, the values of these prognostic factors are inconsistent and remain controversial. Baiocchi et al reported that diffuse histology was an independent predictor of advanced node-negative GC patients,[6] Wang et al reported that anemia was an independent predictor of early GC,[32] Chou et al reported that tumor location and perineural invasion were both independent predictors,[7] and Jin et al reported that lymphovascular invasion was an independent predictor.[8] A possible explanation is that these factors may exert different effects on the timing of cancer recurrence.

Previous studies have shown that patients who experience early recurrence of a variety of malignancies have a poor prognosis.[33-35] However, evidence-based definitions for the early recurrence of GC after radical gastrectomy are few. In the present study, we used PRS as the outcome indicator and demonstrated an optimal cutoff of 24 months for differentiating between early and late recurrence. In the present study, the results of the competing risk model and landmark analysis revealed that diffuse histology, perineural invasion, and anemia were independently associated with early recurrence, while tumor location and lymphovascular invasion were independently associated with late recurrence. However, these associations have not been observed in patients with node-positive GC, which highlights the unique patterns of recurrence in node-negative GC. Thus, more intensive follow-up should be performed during the first two years after surgery in patients with diffuse tumor, perineural invasion, and anemia, and should be performed after 2 years in patients with mixed tumor location and lymphovascular invasion. Moreover, although statistical significance was not reached (P=.079), patients with a high risk of early recurrence may benefit from adjuvant therapy. However, the efficacy of adjuvant chemotherapy seemed limited for patients with a high risk of late recurrence. In this regard, intensive follow-up and early detection of recurrence may help achieve a better prognosis.[36,37]

This study has several limitations. First, as a retrospective study, it may have been subjected to selection bias. Second, despite the multicenter nature, recurrence in node-negative GC remains a rare entity; thus, it may be insufficiently powered to detect true differences. Nevertheless, this study may provide a direction for further investigations into the prognostic stratification of patients with recurrence. Third, we only used data from East Asia. Large samples of data from the West are needed to further validate our findings. However, in Western countries, D1/D1+ lymphadenectomy is performed to treat the majority of patients compared with countries in East Asia where D2 lymphadenectomies are routinely performed, which creates a doubt as to whether the study population was really "node-negative." In contrast, all patients in the present study received standard D2 lymphadenectomies, and none had fewer than 15 lymph nodes, which increased the reliability of our findings. Fourth, we lacked data on dietary factors (e.g., dietary N-nitroso compounds, diet low in fruits and vegetables, and high-salt diet) and cancer-related genes such as p53. Further studies are warranted to demonstrate their associations with early and late recurrence. Finally, this study did not include patients who received neoadjuvant therapy. It is well recognized that patients often experience tumor and lymph node regression and fibrotic response after neoadjuvant therapy.[38] The timing of early recurrence and its influencing factors in patients with node-negative GC who have undergone neoadjuvant therapy warrants further investigation.

In conclusion, we demonstrated that several clinicopathological factors, which have previously been identified as prognostic factors, play different roles in the recurrence of node-negative GC following radical resection. Diffuse tumors, advanced T stage, perineural invasion, and anemia were significantly associated with early recurrence. In contrast, mixed tumor location, advanced T stage, lymphovascular invasion, and elevated CA19-9 levels were significantly associated with late recurrence. This finding may assist with decision-making regarding therapeutic and follow-up strategies for patients with node-negative GC.

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