

## Original Article



## OPEN ACCESS

Received: Jan 25, 2024

Revised: Mar 8, 2024

Accepted: Mar 13, 2024

Published online: Mar 26, 2024

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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# Role of Recurrence Pattern Multiplicity in Predicting Post-recurrence Survival in Patients Who Underwent Curative Gastrectomy for Gastric Cancer

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## ABSTRACT

**Purpose:** This study aimed to investigate the recurrence patterns in patients who underwent curative surgery for gastric cancer (GC) and analyze their prognostic value for post-recurrence survival (PRS).

**Materials and Methods:** We retrospectively reviewed the medical records of 204 patients who experienced GC recurrence following curative gastrectomy for GC at a single institution between January 2012 and December 2017. Specific recurrence patterns (lymph node, peritoneal, and hematogenous) and their multiplicity were analyzed as prognostic factors of PRS.

**Results:** The median PRS of the 204 patients was 8.3 months (interquartile range [IQR]: 3.2–17.4). For patients with a single recurrence pattern (n=164), the difference in each recurrence pattern did not show a significant prognostic value for PRS (lymph node vs. peritoneal, P=0.343; peritoneal vs. hematogenous, P=0.660; lymph node vs. hematogenous, P=0.822). However, the patients with a single recurrence pattern had significantly longer PRS than those with multiple recurrence patterns (median PRS: 10.2 months [IQR: 3.7–18.7] vs. 3.9 months [IQR: 1.8–10.4]; P=0.037). In the multivariate analysis, multiple recurrence patterns emerged as independent prognostic factors for poor PRS (hazard ratio, 1.553; 95% confidence interval, 1.092–2.208; P=0.014) along with serosal invasion, recurrence within 1 year after gastrectomy, and the absence of post-recurrence chemotherapy.

**Conclusions:** Regardless of the specific recurrence pattern, multiple recurrence patterns emerged as independent prognostic factors for poor PRS compared with a single recurrence pattern.

**Keywords:** Gastric cancer; Gastrectomy; Recurrence; Prognosis

## INTRODUCTION

Gastric cancer (GC) is the fifth most commonly diagnosed cancer and the third or fourth leading cause of cancer-related mortality globally [1,2]. Treatment outcomes have improved in recent decades owing to advances in early diagnosis, radical surgery, and adjuvant chemotherapy [3,4]. However, recurrence after curative treatment is often associated with poor prognosis, especially when it cannot be cured by secondary surgery [5]. Despite the prognostic challenges posed by recurrence, patients and their families seek detailed information regarding their life expectancy following recurrence. Consequently, researchers

C.S.J.; Visualization: Y.J.Y.; Writing - original draft: Y.J.Y.; Writing - review & editing: L.W.K.

have investigated various prognostic factors affecting post-recurrence survival (PRS). Most prognostic factors, including pathological results, are established at the time of primary surgery, while some factors related to recurrence status, such as pattern, timing, and treatment, become apparent at the time of recurrence.

GC recurrence typically presents in lymph node (LN), peritoneal, and hematogenous patterns depending on the route of tumor spread [6-9]. Previous studies have reported the incidence, risk factors, and timing of recurrence. However, the prognostic values of these recurrence patterns have rarely been investigated. One study indicated a significant association between peritoneal recurrence pattern and poor PRS in patients with a single recurrence pattern [6]. Another study reported that multiple recurrence patterns tended to correlate with poor prognosis compared with a single pattern [10]. To the best of our knowledge, only a few studies have evaluated the recurrence pattern as a prognostic factor for PRS through multivariate analysis [7].

Hence, this study aimed to investigate the recurrence patterns in patients who underwent curative surgery for GC and analyze their prognostic value for PRS using multivariate analysis, considering other factors defined at the time of primary surgery or recurrence.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed the medical records of 1,587 patients who underwent GC surgery at a single institution (Gachon University Gil Medical Center, Incheon, South Korea) between January 2012 and December 2017 (**Fig. 1**). Among them, those who underwent palliative surgery or exploration only (n=83) or incomplete resection (R1 or R2) (n=21) were excluded. Of the 1,483 patients who underwent curative gastrectomy, 23 were lost to follow-up, and 1,242 did not experience recurrence. Of the 218 patients who experienced recurrence, those with a histology other than adenocarcinoma (n=5) and recurrence at the anastomosis site or remnant stomach (n=9) were excluded. Therefore, the remaining 204 patients were enrolled in the study and followed up until December 31, 2022 (cutoff date). This study was approved by the Institutional Review Board (IRB) of Gachon University Gil Medical Center (IRB No. GFIRB2023-412) and was conducted in accordance with the 1964 Declaration of Helsinki and its later versions. The requirement for written informed consent was waived by the IRB.

### Treatments and follow-up

Patients underwent distal or total gastrectomy depending on the longitudinal location of the tumor within the stomach. The pathological results were analyzed based on the American Joint Committee on Cancer 8th edition criteria [11]. Postoperative complications were graded using the Clavien-Dindo classification, and only severe complications of grade III or higher were included in this study [12]. Patients with tumor, node, metastasis (TNM) stage II or III disease were recommended adjuvant chemotherapy, except in patients with poor performance status or who refused such treatment. After surgery, the patients were followed up every 3 months for the first 2 years and every 6 months for the subsequent 3 years [13]. Complete blood count, liver function, and tumor markers, including carcinoembryonic antigen and carbohydrate antigen 19-9, were assessed at each visit. Abdominal computed tomography (CT) was performed every 6 months for the first 2 years and annually thereafter. Upper gastrointestinal endoscopy was performed annually for 5 years postoperatively. When

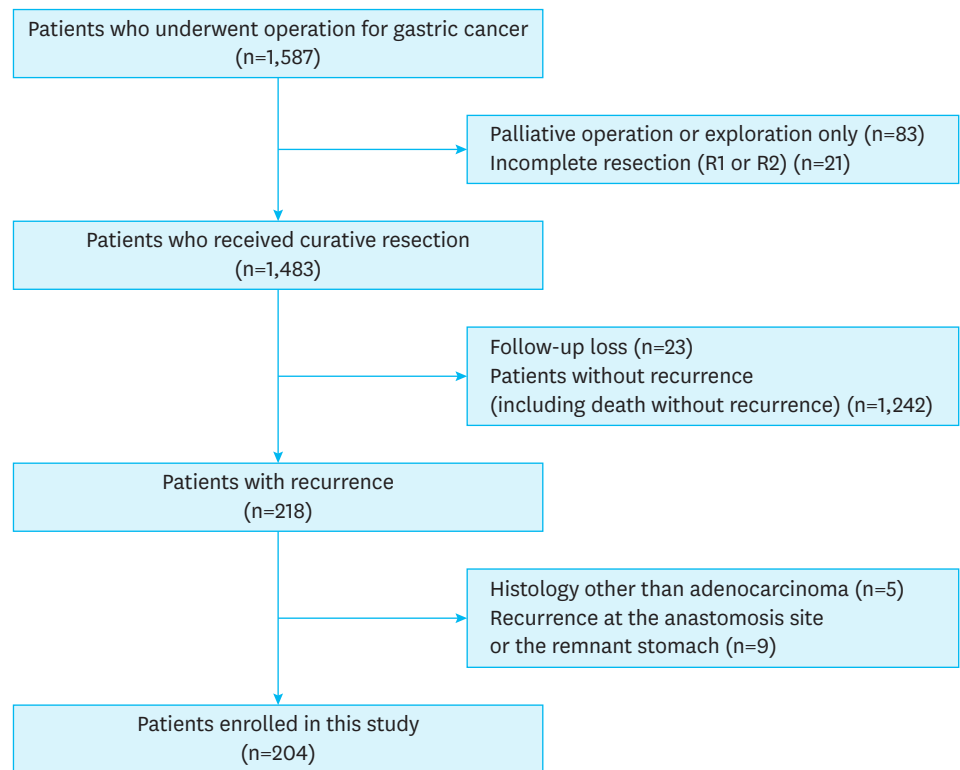


Fig. 1. Flow diagram illustrating the study participants' selection process.

recurrence was suspected, further examinations such as positron emission tomography, magnetic resonance imaging, or surgical exploration were performed to confirm suspected findings. When recurrence was confirmed, the decision to administer chemotherapy was determined based on the patient's performance and consent status.

### Recurrence patterns

For patients with recurrence, we retrospectively reviewed the results of all previously performed examinations using imaging modalities before the date of diagnosis. If the previous examination showed an early recurrence that had been missed during the recent examination, the date of the previous examination was defined as the date of the initial detection of recurrence. Specific data regarding delayed detection of recurrence are described in **Supplementary Table 1**. In our study, the initial recurrence was confirmed by reviewing the results of previous imaging modalities, without requiring histological confirmation. The elevated levels of tumor markers have not been associated with recurrence. Recurrence patterns were classified as LN, peritoneal, or hematogenous based on the route of tumor spread. LN recurrence was defined as the presence of LN enlargement in the retropancreatic, para-aortic, mesenteric root, or distant extra-abdominal area through lymphatic spread. Peritoneal recurrence was defined as the presence of nonlymphatic peritoneal soft tissue, ascites, or Krukenberg tumors through peritoneal implantation. Hematogenous recurrence was defined as the presence of metastatic lesions in the liver, lungs, bones, and other distant organs through hematogenous spread.

### Statistical analysis

Numbers were expressed as median values with interquartile range (IQR) because our data did not show a normal distribution. The clinicopathological characteristics were analyzed using the  $\chi^2$  test or Fisher's exact test. PRS was calculated from the date of initial detection of recurrence to the date of death from any cause. Patient survival was evaluated using the Kaplan-Meier method with a log-rank test. The prognostic factors were evaluated using a Cox proportional hazards model. Variables that were significant in the univariate analysis were included and subsequently selected using the likelihood forward method in the multivariate analysis. All analyses were performed using IBM SPSS Statistics software (version 20.0; IBM Corp., Armonk, NY, USA), and a P-value of <0.050 was considered significant.

## RESULTS

### Clinicopathological characteristics

The clinicopathological characteristics of the 204 patients who developed recurrence after curative gastrectomy for GC are shown in **Table 1**. The median primary tumor size was 6.0 cm (IQR: 4.2–8.7). A total of 137 patients (67.1%) had serosa-positive tumors, while 178 patients (87.3%) had LN metastases. Bormann type IV, diffuse/mixed type, and lymphovascular invasion were detected in 23.5%, 70.1%, and 86.8% of patients, respectively. Overall, 154 patients (75.5%) had TNM stage III disease. Adjuvant chemotherapy was administered in 155 (76.0%) patients. The median time from surgery to recurrence was 12.9 months (IQR: 7.5–24.5). After recurrence, 126 patients (61.8%) received chemotherapy, while 78 (38.2%) received supportive care alone. The chemotherapy regimens administered after recurrence are described in **Supplementary Table 2**. Trastuzumab was administered in 18 (8.8%) patients; their human epidermal growth factor receptor 2 status is described in **Supplementary Table 3**.

### Recurrence patterns

The initial recurrence patterns are illustrated in **Fig. 2**. Among the 204 patients, 164 (80.4%) experienced a single recurrence pattern, 40 (19.6%) experienced multiple recurrence patterns, and 9 (4.4%) presented all three recurrence patterns. Peritoneal recurrence was predominant among those with a single recurrence pattern (52.0%), followed by hematogenous recurrence (15.7%) and LN recurrence (12.7%). Regardless of the recurrence pattern, the liver was the most common site for hematogenous recurrence, followed by the bones, lungs, and brain (**Supplementary Table 4**).

The detailed characteristics of 164 patients with a single recurrence pattern according to the specific recurrence pattern are provided in **Supplementary Table 5**. Female patients were significantly more prevalent in the peritoneal recurrence group than in the LN recurrence group ( $P=0.020$ ). Additionally, the peritoneal recurrence group showed higher proportions of patients with serosa-positive and diffuse/mixed types compared with the hematogenous recurrence group ( $P=0.029$  and  $P=0.033$ , respectively). No significant differences were observed in specific recurrence patterns. A comparison of the characteristics of patients with single and multiple recurrence patterns is outlined in **Supplementary Table 6**. No significant differences were observed in the overall characteristics between patients with a single recurrence pattern and those with multiple recurrence patterns.

**Table 1.** Characteristics of patients who developed recurrence after curative gastrectomy for gastric cancer

Variables	Patients with recurrence (n=204)
Age (yr)	64 (55–74)
Sex	
Male	135 (66.2)
Female	69 (33.8)
ASA score	
1	23 (11.3)
2	156 (76.5)
3	25 (12.3)
Type of surgery	
Distal gastrectomy	92 (45.1)
Total gastrectomy	112 (54.9)
Type of approach	
Open	175 (85.8)
Laparoscopic	29 (14.2)
Tumor size (cm)	6.0 (4.2–8.7)
Borrmann type IV	
Present	48 (23.5)
Absent	156 (76.5)
T stage*	
T1	9 (4.4)
T2	17 (8.3)
T3	41 (20.1)
T4	137 (67.2)
N stage*	
N0	26 (12.7)
N1	29 (14.2)
N2	40 (19.6)
N3	109 (53.5)
TNM stage*	
I	10 (4.9)
II	40 (19.6)
III	154 (75.5)
Lauren classification	
Intestinal	61 (29.9)
Diffuse/mixed	143 (70.1)
Lymphovascular invasion	
Yes	177 (86.8)
No	27 (13.2)
Postoperative complications <sup>†</sup>	
Yes (≥grade III)	25 (12.3)
No	179 (87.7)
Adjuvant chemotherapy	
Yes	155 (76.0)
No	49 (24.0)
Time from surgery to recurrence (mon)	12.9 (7.5–24.5)
Post-recurrence chemotherapy	
Yes	126 (61.8)
No (supportive care alone)	78 (38.2)
Trastuzumab administration	
Yes	18 (8.8)
No	186 (91.2)

Values are presented as median (interquartile range) or number (%).

ASA = American Society of Anesthesiologists; TNM = tumor, node, metastasis.

\*According to the American Joint Committee on Cancer 8th edition; <sup>†</sup>According to the Clavien-Dindo classification.

The PRS according to the recurrence pattern is shown in **Fig. 3**. The median duration of follow-up from recurrence in all 204 patients was 8.3 months (IQR: 3.2–17.4). For

patients with a single recurrence pattern, the differences in each recurrence pattern did not show a significant prognostic value for PRS (LN vs. peritoneal,  $P=0.343$ ; peritoneal vs. hematogenous,  $P=0.660$ ; LN vs. hematogenous,  $P=0.822$ ) (Fig. 3A). In patients with hematogenous recurrence only, the PRS was not affected by the specific site of metastasis ( $P=0.616$ ) (Supplementary Fig. 1). However, irrespective of each recurrence pattern, patients with a single recurrence pattern experienced a significantly longer PRS than those with multiple recurrence patterns (median PRS: 10.2 months [IQR: 3.7–18.7] in patients with single recurrence pattern vs. 3.9 months [IQR: 1.8–10.4] in those with multiple recurrence patterns;  $P=0.037$ ) (Fig. 3B). Furthermore, as the number of recurrence patterns increased,

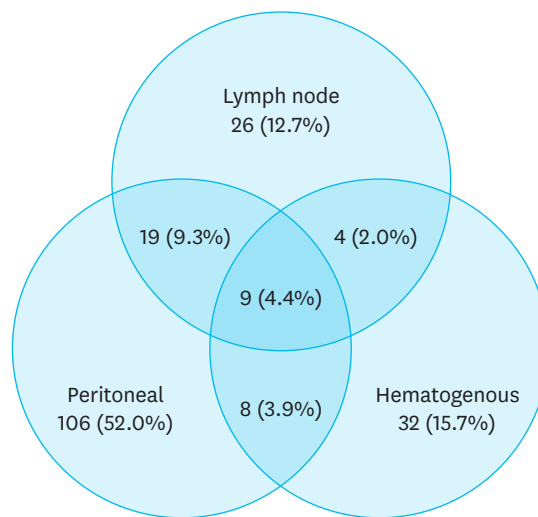


Fig. 2. Distribution of recurrence patterns among patients who underwent curative gastrectomy for gastric cancer.

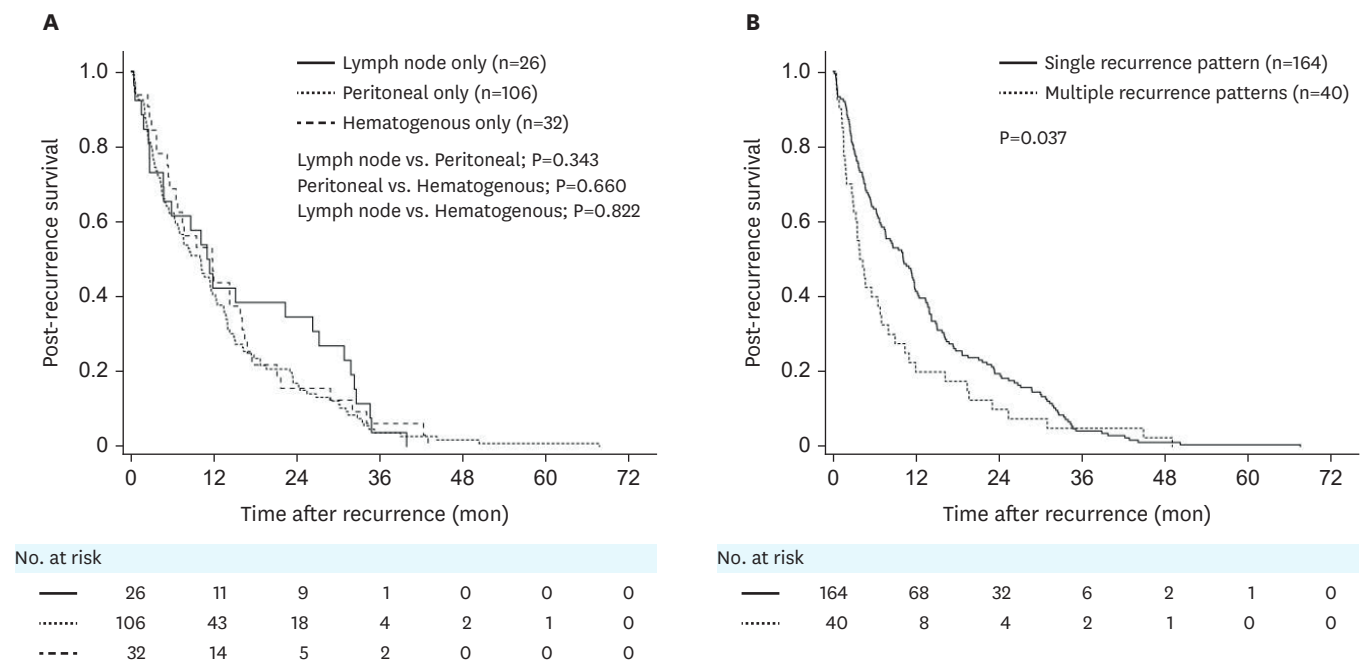


Fig. 3. Comparison of post-recurrence survival (A) according to specific recurrence patterns in patients with a single recurrence pattern (B) and between patients with single and multiple recurrence patterns.

the PRS of the patients showed a decreasing trend ( $P=0.010$ ) (Supplementary Fig. 2). The recurrence-free survival (RFS) according to the recurrence pattern (Supplementary Fig. 3), showing no impact of specific recurrence patterns or their multiplicity on RFS.

### Time from surgery to recurrence and the administration of post-recurrence chemotherapy

The PRS according to the time from surgery to recurrence and the administration of post-recurrence chemotherapy is shown in Fig. 4. Patients experiencing recurrence within 1 year following gastrectomy exhibited significantly shorter PRS than those with recurrence after 1 year (median PRS: 5.6 months [IQR: 2.7–11.6] vs. 12.3 months [IQR: 4.3–17.4];  $P<0.001$ ) (Fig. 4A). Additionally, patients who received post-recurrence chemotherapy experienced significantly longer PRS than those who received supportive care alone (median PRS: 12.2 months [IQR: 6.5–23.4] vs. 3.1 months [IQR: 1.6–6.9];  $P<0.001$ ) (Fig. 4B). Patients who received adjuvant chemotherapy appeared to exhibit slightly poorer PRS, both with and without post-recurrence chemotherapy, although this trend was not significant ( $P=0.219$  and  $P=0.417$ , respectively) (Supplementary Fig. 4).

### Prognostic factors for PRS

Table 2 presents the prognostic factors for PRS. In the univariate analysis, age  $\geq 65$  years, serosa invasion, multiple recurrence patterns, recurrence within 1 year after gastrectomy, and the absence of post-recurrence chemotherapy were identified as poor prognostic factors for PRS. In the multivariable analysis, serosa invasion (hazard ratio [HR], 1.559; 95% confidence interval [CI], 1.154–2.106;  $P=0.004$ ), multiple recurrence patterns (HR, 1.553; 95% CI, 1.092–2.208;  $P=0.014$ ), recurrence within 1 year after gastrectomy (HR, 1.483; 95% CI, 1.113–1.977;  $P=0.007$ ), and the absence of post-recurrence chemotherapy (HR, 2.973; 95% CI, 2.184–4.047;  $P<0.001$ ) emerged as independent prognostic factors for poor PRS.

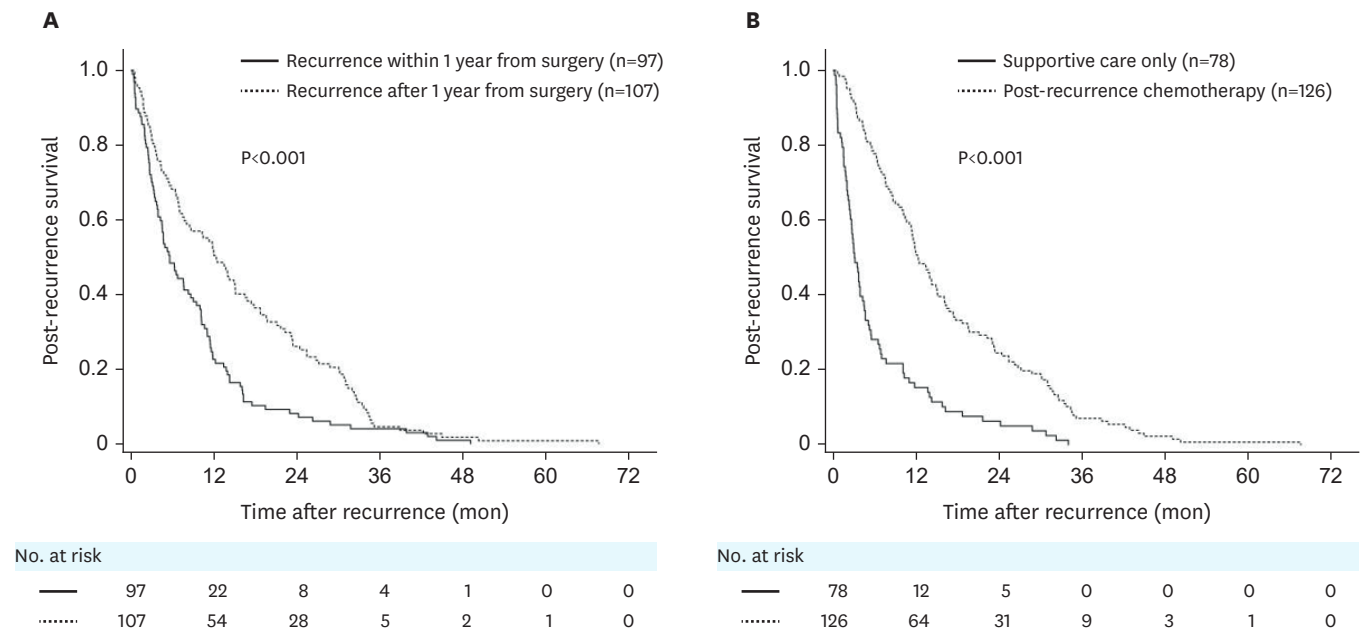


Fig. 4. Comparison of post-recurrence survival according to (A) time from surgery to recurrence and (B) post-recurrence chemotherapy administration.



**Table 2.** Prognostic factors for post-recurrence survival

Variables	No.	Univariable		Multivariable	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age			0.035		
<65 years	105	1			
≥65 years	99	1.348 (1.022–1.779)			
Sex			0.604		
Male	135	1			
Female	69	0.925 (0.689–1.242)			
ASA score			0.082		
1, 2	179	1			
3	25	1.455 (0.954–2.219)			
Type of surgery			0.822		
Distal gastrectomy	92	1			
Total gastrectomy	112	0.969 (0.734–1.278)			
Type of approach			0.924		
Open	175	1			
Laparoscopic	29	0.981 (0.661–1.455)			
Tumor size			0.073		
<5 cm	63	1			
≥5 cm	141	1.316 (0.974–1.778)			
Borrmann type IV			0.258		
Absent	156	1			
Present	48	1.207 (0.871–1.672)			
Serosa invasion			0.048		0.004
Negative	67	1		1	
Positive	137	1.346 (1.002–1.808)		1.559 (1.154–2.106)	
LN metastasis			0.516		
Negative	26	1			
Positive	178	1.147 (0.758–1.733)			
TNM stage*			0.065		
I, II	50	1			
III	154	1.359 (0.981–1.882)			
Lauren classification			0.112		
Intestinal	61	1			
Diffuse/mixed	143	1.277 (0.945–1.727)			
Lymphovascular invasion			0.552		
No	27	1			
Yes	177	0.884 (0.588–1.328)			
Postoperative complications†			0.602		
No	179	1			
Yes (≥grade III)	25	0.893 (0.583–1.367)			
Adjuvant chemotherapy			0.876		
No	49	1			
Yes	155	0.975 (0.705–1.347)			
Recurrence pattern			0.039		0.014
Single pattern	164	1		1	
Multiple patterns	40	1.446 (1.019–2.051)		1.553 (1.092–2.208)	
Time from surgery to recurrence			<0.001		0.007
>1 year	107	1		1	
≤1 year	97	1.722 (1.298–2.284)		1.483 (1.113–1.977)	
Post-recurrence chemotherapy			<0.001		<0.001
Yes	126	1		1	
No (supportive care alone)	78	2.832 (2.104–3.811)		2.973 (2.184–4.047)	
Trastuzumab administration			0.078		
Yes	18	1			
No	186	1.551 (0.952–2.528)			

HR = hazard ratio; CI = confidence interval; ASA = American Society of Anesthesiologists; LN = lymph node; TNM = tumor, node, metastasis.

\*According to the American Joint Committee on Cancer 8th edition; †According to the Clavien-Dindo classification.



## DISCUSSION

Our study results revealed that the prognosis of patients who experienced GC recurrence was not affected by a specific recurrence pattern but rather by the multiplicity of recurrence patterns. Patients with multiple recurrence patterns had a significantly shorter PRS than those with a single recurrence pattern. In the multivariate analysis, along with multiple recurrence patterns, serosal invasion of the primary tumor, recurrence within 1 year from primary surgery, and the absence of post-recurrence chemotherapy were independent prognostic factors for poor PRS. Among these independent prognostic factors, serosal invasion of the primary tumor was determined at the time of primary surgery, while the other three prognostic factors were newly identified at the time of recurrence.

Some studies have highlighted the prognostic value of specific recurrence patterns, with peritoneal recurrence often associated with poorer prognosis [5-7,10]. Sawaki et al. [6] reported that patients with peritoneal recurrence patterns had significantly shorter PRS than those with LN or hematogenous recurrence patterns. This result was attributed to late detection during postoperative follow-up and limitations in the sensitivity of the imaging modalities [6]. However, our study found similar prognoses after recurrence among patients with three specific recurrence patterns. The discrepancy in the previous results could be due to the differences in the definition of the date of recurrence. Our study determined the date of the initial detection of recurrence through a retrospective review of the results of previous imaging examinations. Therefore, our initial date of recurrence may have been earlier than those reported in previous studies, especially in cases of peritoneal recurrence. Although specific recurrence patterns were not identified as significant prognostic factors in our study, the multiplicity of recurrence patterns was a significant predictor of PRS. These results are consistent with those of previous studies, suggesting that multiple recurrence patterns may have a greater tumor burden than a single recurrence pattern [7,10,14,15].

In addition to recurrence patterns, recurrence within 1 or 2 years after primary surgery has been associated with poor prognosis in previous studies [7,16-20]. Eom et al. [16] reported that recurrence within 1 year was significantly associated with poor PRS, possibly due to tumor aggressiveness and potential systemic metastasis during surgery. We speculate that the inherent aggressiveness of tumors, not fully represented by the TNM stage, may affect the speed of progression after primary surgery and the subsequent prognosis after recurrence. Several studies have also identified early recurrence as an independent prognostic factor for poor PRS in the multivariate analysis, considering other factors associated with the TNM stage of the primary tumor [17,19,20]. Early recurrence has similarly been highlighted as a significant factor for poor prognosis in other tumors, including colorectal, breast, liver, and pancreas cancer [21-24].

In our study, although not significant, adjuvant chemotherapy tended to have a slightly negative effect on the PRS in both patients with and without post-recurrence chemotherapy. A previous study speculated that this finding could stem from acquired resistance to adjuvant chemotherapy and the detrimental effects of chemotherapy on patient immunity [7]. However, the administration of post-recurrence chemotherapy emerged as a significant prognostic factor for PRS. Furthermore, the use of trastuzumab after recurrence tended to be associated with a longer PRS in the univariate analysis ( $P=0.078$ ). Previous studies have reported that although secondary surgery might not be feasible for recurrent GC, palliative chemotherapy could prolong survival after recurrence [7,19,25,26]. The beneficial role of

post-recurrence chemotherapy has also been reported in patients with colorectal cancer [27]. We speculate that these results may be attributed to the favorable performance status of patients eligible for active systemic treatment after recurrence as well as the therapeutic effects of chemotherapy.

Among the pathological factors defined at the time of primary surgery, serosal invasion (T4) remained a significant prognostic factor after recurrence; however, N and TNM stages were not significant in our study. Previous studies have presented conflicting findings concerning the predictive role of the pathological stage of primary tumors on prognosis after recurrence [8,16-19]. Takahashi et al. reported that the pathological stage did not significantly affect prognosis after recurrence, although the frequency of recurrence was dependent on the pathological stage [8]. One possible explanation is that the majority of patients with recurrence already have advanced pathological stages that cannot significantly differentiate their prognosis after recurrence. Recurrence explains the biological aggressiveness of the tumor, irrespective of the primary tumor stage. Li et al. [17] suggested that the aggressiveness of recurrent lesion growth might differ from that of primary tumors.

Our study has several limitations. First, it was a retrospective study conducted at a single institution. Second, caution is needed when interpreting our results due to the potential for type II error resulting from the small cohort size compared with previous studies. Third, although all imaging examinations were reviewed by an experienced radiologist (SJC) at our institution, who was also a member of our multidisciplinary team, this may introduce bias as the reviewer was not an independent investigator. Fourth, the date of recurrence was defined as the examination date of the imaging modality that initially detected the recurrence. Considering our postoperative follow-up schedule of 3–6 months, the results regarding PRS time should be viewed within a clinical context rather than as indicative of true biological phenomena. Consequently, external validation of our study findings is warranted through a large prospective study that includes a more intensive follow-up and more sensitive methods to detect recurrence.

In conclusion, irrespective of the specific recurrence pattern, multiple recurrence patterns were independent prognostic factors for poor PRS compared with a single recurrence pattern. Furthermore, serosal invasion of the primary tumor, recurrence within 1 year after the primary surgery, and the absence of post-recurrence chemotherapy were independent prognostic factors for poor PRS. These prognostic factors, defined at the time of primary surgery or recurrence, could be useful for counseling patients regarding recurrence in clinical practice.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Delayed detections of recurrences according to recurrence pattern (n=204)

### Supplementary Table 2

Chemotherapeutic regimens used after recurrence (n=126)

### Supplementary Table 3

HER2 status in patients with gastric cancer recurrence (n=204)

**Supplementary Table 4**

Specific sites of hematogenous recurrence (n=53)

**Supplementary Table 5**

Patient characteristics according to the specific recurrence pattern in patients with a single recurrence pattern (n=164)

**Supplementary Table 6**

Patient characteristics between patients with single and multiple recurrence patterns (n=204)

**Supplementary Fig. 1**

Comparison of post-recurrence survival according to specific sites of metastasis in patients with hematogenous recurrence only.

**Supplementary Fig. 2**

Comparison of post-recurrence survival according to the number of recurrence patterns.

**Supplementary Fig. 3**

Comparison of recurrence-free survival (A) according to the specific recurrence pattern in patients with a single recurrence pattern (B) between patients with single and multiple recurrence patterns.

**Supplementary Fig. 4**

Comparison of post-recurrence survival according to receiving adjuvant chemotherapy and post-recurrence chemotherapy.

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