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Stage-specific difference in timing and pattern of initial recurrence after curative surgery for gastric cancer

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ABSTRACT

Background: Gastric cancer (GC) follow-up schedule after curative surgery is universally recommended based on the pathologic stage, but their details, including intervals and modalities of surveillance have not yet been standardised. The aim of this study was to investigate the characteristics of GC recurrence by stage to establish optimal postoperative surveillance strategies.

Methods: Medical information on 5095 patients with GC who underwent curative intent gastrectomy in our institution between January 1989 and December 2013 was reviewed retrospectively. Moreover, 656 patients who had recurrences after radical surgery were identified. Clinicopathologic characteristics, timing and pattern of recurrence, and survival data of these patients were analysed.

Results: Among the 656 patients, 50 (7.6%), 123 (18.8%), and 483 (73.6%) had stages I, II, and III GC, respectively. The median times to initial recurrence in patients with stages I, II, and III GC were 23.5 months (interquartile range [IQR], 13.0–33.0 months), 13.0 months (IQR, 9.0–25.0 months), and 12.0 months (IQR, 7.0–21.0 months), respectively. In patients with stage I GC, more than half (58%) of them had distant organ metastasis; otherwise, peritoneal dissemination (39%) was the most common pattern in patients with stage III GC.

Conclusions: Despite the low incidence, the time of initial recurrence in stage I GC was longer than those in stage II and III GC. Moreover, the pattern of initial recurrence was also different according to the pathologic stage. Therefore, clinicians should consider stage-specific differences of recurrence in setting up surveillance strategies after curative surgery for GC patients.

1. Introduction

Recently, the survival rate of patients with gastric cancer (GC) has increased significantly due to advances in diagnostic techniques and treatment modalities [1,2]. However, it still remains the third most frequent cause of cancer-related deaths worldwide [3]. Moreover, chemotherapy and radiotherapy are less effective against GC than against other solid malignancies because of the heterogeneity of GC [4,5]. It is hard to expect good response to treatment after recurrence or metastasis for GC, and the outcomes of treatment after recurrence are similar for early- and advanced-stage GC. Recent clinical trial results reveal that the median overall survival for patients treated with cytotoxic chemotherapy for metastatic disease is less than one year [6–8]. Therefore, early detection of GC recurrence as well as initial treatment such as gastrectomy and adjuvant chemotherapy is critical in achieving a good prognosis.

In general, the treatment and surveillance of patients after curative gastrectomy are conducted separately based on the pathologic stage [9,10]. However, the follow-up schedule for GC patients has not yet been standardised worldwide, and most centres manage patients according to institution-specific protocols [11]. In addition, there is a great diversity in institutional follow-up programs for stage I GC patients, because of the low recurrence rate (1.5–12%) compared to patients with stage II or III GC [12–14].

In this study, we evaluated stage-specific difference in timing and pattern of initial recurrence in GC patients who underwent curative gastrectomy and sought to identify the optimal surveillance strategies for GC patients based on pathologic stage.

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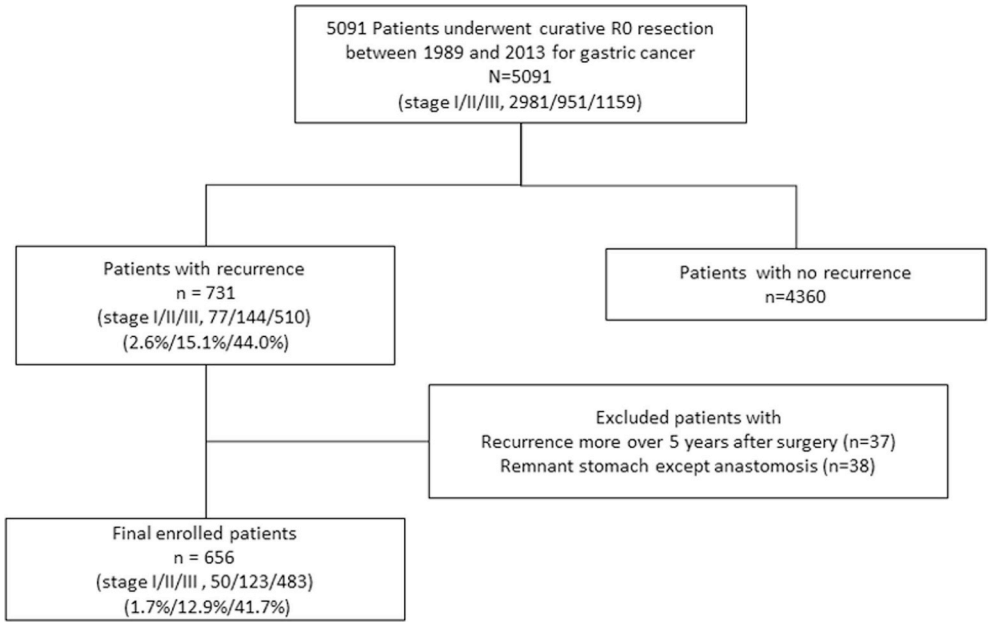

Fig. 1. Patient flow diagram of this study.

2. Methods

2.1. Patients and data collection

Data on 5095 patients with GC who underwent curative intent gastrectomy at Seoul St. Mary's Hospital, The Catholic University of Korea, between January 1989 and December 2013 were reviewed. All patients were pathologically proven to have gastric adenocarcinoma, and disease staging and histopathologic classification were based on the seventh edition of the American Joint Committee on Cancer staging system [15]. Patients who had metastatic disease at the time of surgery and undergone non-curative resection or been treated with preoperative chemotherapy or radiotherapy were excluded from the study. Among them, 731 who had recurrences were identified. In addition, 75 patients in whom GC recurred in the remnant stomach or ≥5 years after surgery were excluded to rule out synchronous and metachronous cancers. Ultimately, data on 656 patients were analysed (Fig. 1). Clinicopathologic data (sex, age, tumour location, depth of invasion, lymph node (LN) metastasis, TNM stage, histological classification, and surgical procedure) were obtained by retrospective review of the medical records. The study was approved by the ethics committee of the Institutional Review Board of our institution.

2.2. Treatment and follow-up evaluation

All enrolled patients underwent subtotal or total gastrectomy with adequate LN dissection (D1+ or D2). Postoperative chemotherapy was performed according to disease stage and the physical condition and willingness of the patient. The regimens of adjuvant chemotherapy were primarily fluoropyrimidine- or platinum-based combinations. In our institution, the follow-up schedule for patients with GC differs depending on the pathologic stage Patients with stage I GC are followed every 6 months until 3 years after surgery and then annually up to 5 years or until death. Patients with stage II or III GC are followed every 3 months until 3 years after surgery, every 6 months up to 5 years, and then annually or until death. The follow-up evaluation involves taking of a medical history, physical examination, chest radiography, laboratory parameters and tumour markers, and abdominal computed tomography (CT). Endoscopy and bone scan were performed annually during follow-up period. The median follow-up period was 73 months.

Recurrence was diagnosed based on radiological findings or biopsies of suspicious lesions. The patterns of initial recurrence were stratified into four groups: loco-regional (including recurrence in the remnant stomach and anastomosis site and regional LN metastasis), distant LN, distant organs (e.g. liver, lung, bone), and peritoneal dissemination. After a diagnosis of recurrence, patients usually receive systemic chemotherapy. Patients who died without known tumour recurrence were censored at the last documented evaluation.

2.3. Statistical analysis

Discrete and categorical variables are expressed as counts with percentages, and continuous variables as means with standard deviations. Univariate comparisons according to macroscopic appearance were performed by analysis of variance or Kruskal–Wallis test, as appropriate. P-values < 0.05 were deemed indicative of statistical significance. Statistical analyses were conducted using SPSS version 19 (SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline characteristics of patients

A total of 656 patients with GC who experienced recurrence after curative gastrectomy were analysed. The patient's baseline characteristics are presented in Table 1. Of them, 439 (66.9%) were men and 217 (33.1%) were women, and the patients had a mean age of 58.7 ± 12.2 years (range, 20–85 years). Fifty (7.6%) patients had stage I, 123 (18.8%) patients had stage II, and 483 (73.6%) patients had stage III GC. The patients with advanced-stage GC tended to be younger than those with early-stage GC. Sex and tumour location did not differ significantly among stages. Total gastrectomy with Roux-en-Y reconstruction, large tumour size, undifferentiated histology, diffuse type, lymphovascular invasion, and neural invasion were significantly more frequent in advanced-stage GC compared with early-stage GC.

3.2. Time to initial recurrence according to stage

The peak frequency of the timing of initial recurrence differed by stage (Fig. 2A). In patients with stage I GC, the median time to recurrence after surgery was 23.5 months (interquartile range [IQR], 13.0–33.0 months], whereas 13.0 months (IQR, 9.0–25.0 months) and

Table 1
Clinicopathologic characteristics of patients who had recurrences after curative surgery.

	Stage I (N = 50)	Stage II (N = 123)	Stage III (N = 483)	Total (N = 656)	*P* value
Age	63.5 [58.0; 69.0]	63.0 [52.0; 70.0]	59.0 [50.0; 67.0]	60.0 [50.0; 68.0]	0.002
Sex					
Male	36 (72.0%)	78 (63.4%)	325 (67.3%)	439 (66.9%)	0.523
Female	14 (28.0%)	45 (36.6%)	158 (32.7%)	217 (33.1%)	
Operation					
Total	7 (14.0%)	35 (28.5%)	212 (43.9%)	254 (38.7%)	< 0.001
Subtotal	43 (86.0%)	86 (70.5%)	271 (56.1%)	402 (61.3%)	
Approach					
Open	31 (62.0%)	108 (87.8%)	477 (98.8%)	616 (93.9%)	< 0.001
Laparoscopic	19 (38.0%)	15 (12.2%)	6 (1.2%)	40 (6.0%)	
Lymph node dissection					
D1 +	19 (38.0%)	23 (18.7%)	46 (9.5%)	88 (13.4%)	< 0.001
D2	31 (62.0%)	100 (81.3%)	437 (90.5%)	568 (86.6%)	
Tumor size	3.5 [2.5; 4.8]	5.0 [3.5; 7.0]	6.6 [5.0; 9.0]	6.0 [4.5; 8.5]	< 0.001
Tumor location					0.084
EGJ	1 (2.0%)	1 (0.8%)	5 (1.0%)	7 (1.1%)	
upper	2 (4.1%)	14 (11.5%)	68 (14.2%)	84 (12.9%)	
middle	14 (28.6%)	32 (26.2%)	159 (33.2%)	205 (31.5%)	
lower	32 (65.3%)	74 (60.7%)	232 (48.4%)	338 (52.0%)	
whole	0 (0.0%)	1 (0.8%)	15 (3.1%)	16 (2.5%)	
Proximal cut margin	4.2 [2.8; 6.5]	4.0 [2.5; 6.6]	3.2 [2.0; 5.0]	3.5 [2.0; 5.5]	< 0.001
T stage					
1	36 (72.0%)	16 (13.0%)	0 (0.0%)	52 (7.9%)	
2	14 (28.0%)	28 (22.8%)	36 (7.5%)	78 (11.9%)	< 0.001
3	0 (0.0%)	51 (41.5%)	117 (24.2%)	168 (25.6%)	
4	0 (0.0%)	28 (22.8%)	330 (68.3%)	358 (54.6%)	
N stage					
0	43 (86.0%)	52 (42.3%)	4 (0.8%)	99 (15.1%)	
1	7 (14.0%)	36 (29.3%)	27 (5.6%)	70 (10.7%)	< 0.001
2	0 (0.0%)	30 (24.4%)	101 (20.9%)	131 (20.0%)	
3	0 (0.0%)	5 (4.1%)	351 (72.7%)	356 (54.3%)	
Retrieved lymph nodes	31.0 [21.0; 42.0]	39.0 [28.0; 51.0]	44.0 [34.0; 56.0]	43.0 [32.0; 54.0]	< 0.001
Metastatic lymph nodes	0.0 [0.0; 0.0]	1.0 [0.0; 3.0]	11.0 [6.0; 19.0]	7.5 [2.0; 16.0]	< 0.001
Histology					
Differentiated	27 (54.0%)	57 (46.3%)	156 (32.3%)	240 (36.6%)	< 0.001
Undifferentiated	23 (46.0%)	66 (53.7%)	327 (67.7%)	416 (63.4%)	
Signet ring cell	11 (22.0%)	12 (9.8%)	41 (8.5%)	64 (9.8%)	
Lauren classification					
Intestinal	25 (53.2%)	48 (39.3%)	131 (27.8%)	204 (31.9%)	0.002
Diffuse	14 (29.8%)	45 (36.9%)	227 (48.2%)	286 (44.7%)	
Mixed	8 (17.0%)	29 (23.8%)	113 (24.0%)	150 (23.4%)	
Lymphatic invasion					
None	36 (73.5%)	46 (37.7%)	17 (3.6%)	99 (15.4%)	< 0.001
Yes	13 (26.5%)	76 (62.3%)	454 (96.4%)	543 (84.6%)	
Vascular invasion					
None	45 (93.8%)	109 (89.3%)	371 (78.9%)	525 (82.0%)	0.003
Yes	3 (6.2%)	13 (10.7%)	99 (21.1%)	115 (18.0%)	
Neural invasion					
None	40 (83.3%)	69 (56.6%)	120 (25.4%)	229 (35.7%)	< 0.001
Yes	8 (16.7%)	53 (43.4%)	352 (74.6%)	413 (64.3%)	
Adjuvant chemotherapy					
None	46 (92.0%)	30 (24.4%)	43 (8.9%)	119 (18.1%)	< 0.001
Yes	4 (8.0%)	93 (75.6%)	440 (91.1%)	537 (81.8%)	

Categorical variables are present as number with percentage. Continuous variables are presented as median and interquartile range.

12.0 months (IQR, 7.0–21.0 months) in patients with stages II and III GC, respectively. And, the median time to recurrence in stage I GC was significantly longer than those in stage II and III GC (Stage I vs. stage II, $P = 0.002$; stage II vs. stage III, $P = 0.096$; stage I vs. stage III, $P < 0.001$) (Fig. 2B).

3.3. Pattern of initial recurrence according to stage

More than half of patients with stage I GC experienced distant organ metastasis upon initial recurrence, and peritoneal dissemination was the most frequent pattern in patients with stage III GC. Table 2 presented the recurrence sites according each stage in detail. In patients with stage I GC, the liver (26%) was the most common site of initial recurrence, followed by distant LNs and the peritoneum. In patients with stage II GC, the peritoneum (33%) and liver (30%) showed similar frequency. In patients with stage III GC, the peritoneum (39%) was the most common site of initial recurrence, followed by regional LNs and the liver.

Fig. 3 showed the trends of initial recurrence pattern over time in each stage. In patients with stage I GC, distant organ was most common pattern of recurrence, except for the period between postoperative 1 and 2 years. The recurrence pattern over time in patients with stage II and III GC was similar, in which peritoneum was the most common.

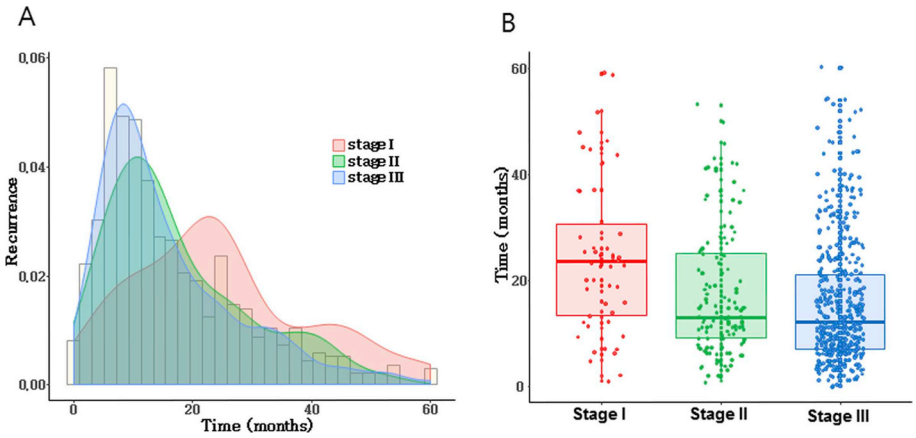

Fig. 2. A. The peak frequency of the timing of initial recurrence after surgery according to stage. B. The median time to recurrence in stage I GC was significantly longer than those in stage II and III GC (Stage I vs. stage II, P = 0.002; stage II vs. stage III, P = 0.096; stage I vs. stage III, P < 0.001).

Table 2
Sites of recurrence and outcome according to stages.

	Stage I (N = 50)	Stage II (N = 123)	Stage III (N = 483)	Total (N = 656)	*P* value
Locoregional	6 (12.0%)	18 (14.6%)	89 (18.4%)	113 (17.2%)	0.002
Lung	6 (12.0%)	4 (3.3%)	26 (5.4%)	36 (5.5%)	
Liver	13 (26.0%)	37 (30.1%)	72 (14.9%)	122 (18.6)	
Bone	4 (8.0%)	3 (2.4%)	27 (5.6%)	34 (5.2%)	
Ovary	0 (0.0%)	0 (0.0%)	6 (1.2%)	6 (0.9%)	
Distant node	8 (16.0%)	15 (12.2%)	57 (11.8%)	80 (12.2%)	
Peritoneal	7 (14.0%)	41 (33.3%)	187 (38.7%)	235 (35.8%)	
Others	6 (12.0%)	5 (4.1%)	19 (3.9%)	30 (4.6%)	

Values in parentheses are percentage.

3.4. Overall survival after recurrence according to stage

The median overall survival duration after recurrence was 7.0 months (IQR, 3.0–15.0 months). Patients with stage I GC had higher 1-, 3-, and 5-year survival rates (52.3%, 28.7%, and 15.3%, respectively) than patients with stage II GC (54.7%, 13.0%, and 8.8%, respectively) and those with stage III GC (36.4%, 6.3%, and 2.1%, respectively). The survival rate after recurrence in stage I GC was significantly higher than those in stage II and III GC (Stage I vs. stage II, P = 0.347; stage II vs. stage III, P = 0.001; stage I vs. stage III, P = 0.001)(Fig. 4).

4. Discussion

The rate of GC recurrence after curative resection is reportedly 15–60% in previous literature. The majority of GC recurrence develops within the first 2 years after surgery [16–18]. Tumour depth, LN metastasis, tumour size, and lymphatic invasion were known as predictive factors associated with recurrence [17–19]. However, previous studies have yet to provide information on differences in the characteristics of recurrence according to stage, while postoperative surveillance of GC is generally based on pathologic stage.

In the present study, the time to initial recurrence was longer in stage I GC than in stage GC. The most frequent recurrence time in patients with stages II and III GC was 13 months, and that of patients with stage I GC was 24 months (IQR, 13–31 months); the latter is in agreement with prior reports (24–34 months). In a retrospective study of node-negative stage I GC, Cao et al. [20] demonstrated that the liver was the most common site of recurrence, and most recurrences were detected between 6 months and 3 years postoperatively. Sano et al. [14] reported that more than 40% of patients with early GC developed recurrences within the first 3 years after surgery, and 23% did so after 5 years. In practice, patients with early-stage GC are likely to undergo less intensive surveillance after 2 years postoperatively than those with advanced-stage GC. The incidence is very low, but if recurrence developed after that period, it could be overlooked. Therefore, clinicians should pay more attention to changes in patient's symptoms and serum level of tumour markers for at least 3 years after surgery even in patients with stage I GC and recommend imaging tests such as ultrasound or CT, if necessary.

Many previous studies reported various results on the patterns of GC recurrence after curative surgery [21–23]. Schwarz et al. [21] found that the most common pattern was distant metastasis (37%), and Yoo et al. [22] found that the most frequent recurrence pattern was peritoneal dissemination (33.9%). In the present study, the pattern of GC recurrence differed according to pathologic stage. In stage I GC, distant organ metastasis, so-called haematogenous metastasis, was the most common pattern of initial recurrence; that in patients with stage III GC was peritoneal dissemination. Patients with stage II GC showed both of these patterns. Discrepancies in the initial recurrence patterns seen in previous studies may be due to stage-specific differences, along with factors associated with recurrence such as tumour depth, location, Lauren 's subtype, and sex [18,24,25]. Therefore, the modalities of follow-up studies should be selected appropriately considering the patient's pathologic stage and risk factors. For example, if the level of a tumour marker is consistently increasing, patients with stage I GC may require ultrasound directed at the liver metastasis; frequent CT examinations and laparoscopic exploration of peritoneal metastasis may be considered in patients with stage III GC.

Even those patients who were initially diagnosed with early-stage GC showed the same rapid clinical deterioration as those diagnosed with stage IV GC after recurrence or metastasis [26,27]. Regarding survival duration after recurrence, Yoo et al. [22] reported that most patients succumbed within 1 year of receiving a diagnosis of recurrence (mean survival, 8.7 [range 2–66] months). In this study, the median survival after recurrence of stage I GC was better than that after stage III GC (8.5 vs. 6.0 months, P < 0.001). Also, more than half of recurrence in stage I GC patients showed haematogenous spread such as liver metastasis. If these recurrences are found early on, various treatments such as surgery or radiotherapy could also be helpful in addition to

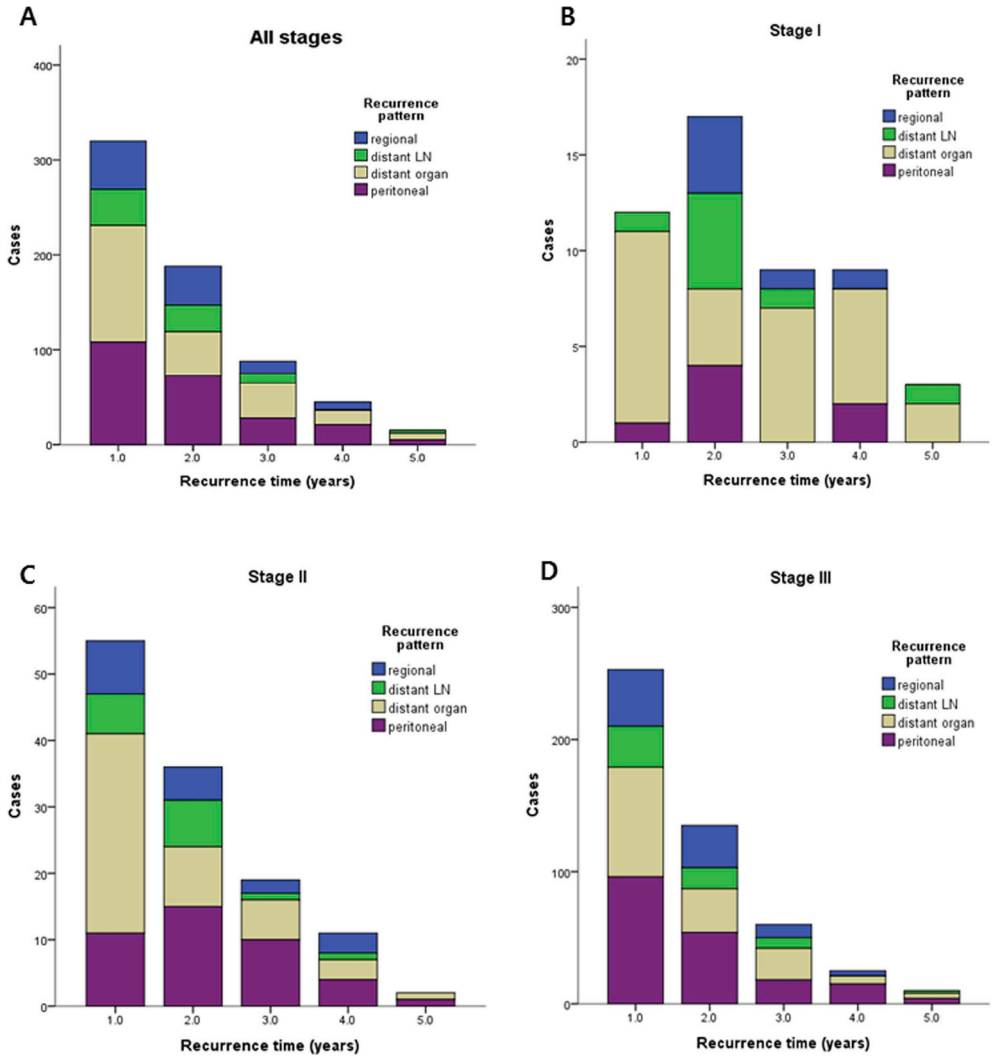

Fig. 3. The distributions of recurrence pattern over time in each stage. (A. all patients, B. stage I, C. stage II, D. stage III).

systemic chemotherapy [28,29].

According to Korea nationwide survey conducted by Hur et al. [11], Korean physicians examine patients with early- and advanced-stage GC every 3 and 6 months, respectively, in the first year postoperatively. In postoperative 2–4 years, patients with GC are typically followed at 6-month intervals. However, the proportion of clinicians who follow patients with early-stage GC at 12-month intervals has increased. In reality, regional variations in health insurance, institutional status, and patient compliance hamper the establishment of a unified surveillance strategy after curative gastrectomy. Furthermore, more intensive surveillance of patients with early GC may not be cost-effective. Therefore, clinical trials evaluating follow-up frequency and modalities should analyse the survival benefit and cost-effectiveness of follow-up surveillance after curative gastrectomy for GC.

This study has several limitations. First, it had a retrospective design and was conducted at a single centre in Korea, so large-scale studies involving Western patients are warranted. Second, data on treatment mortalities after recurrence were excluded because of their heterogeneity. We cannot rule out the possibility that bias affected our findings on survival after recurrence. Because no standard treatment for patients with recurrent GC has been established, well-designed prospective studies are needed to overcome this limitation. In addition, it is important to develop a model for predicting patients at higher risk of recurrence in each stage and to establish a patient-tailored follow-up program. In this study, we analysed the risk factors for recurrence in each stage, but unfortunately failed to create a predictive model because there were a few clinicopathologic variables with statistical significance except for T and N stages (Supplementary Table S1). Further research on precision medicine, such as next-generation sequencing, might to be helpful to develop a more accurate predictive model.

In conclusion, although the incidence was very low, the time of initial recurrence after curative surgery in stage I GC was longer than those in stage II or III GC. Also, the patterns of initial recurrence were different according to stage. Therefore, clinicians should consider stage-specific differences of recurrence when choosing surveillance frequency and modalities after curative surgery for GC.

Conflicts of interest

All authors declare that they have no conflict of interest.

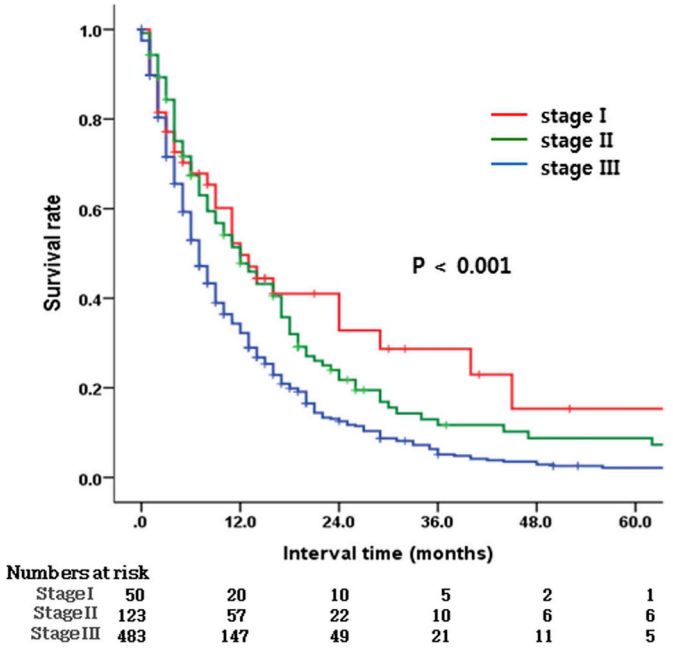

Fig. 4. Kaplan-Meier curve of overall survival after recurrence in patients underwent curative gastrectomy classified by initial pathologic stage. The survival rate after recurrence in stage I GC was significantly higher than those in stage II and III GC (Stage I vs. stage II, P = 0.347; stage II vs. stage III, P = 0.001; stage I vs. stage III, P = 0.001).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.05.023.

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The funding source had no effect on study design, analysis and interpretation of the data, in the writing of the manuscript and in the decision to submit it for publication.

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