JGC | Journal of Gastric Cancer

Original Article

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Tumor Location Causes Different Recurrence Patterns in Remnant Gastric Cancer

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ABSTRACT

Purpose: Tumor recurrence is the principal cause of poor outcomes in remnant gastric cancer (RGC) after resection. We sought to elucidate the recurrent patterns according to tumor locations in RGC.

Materials and Methods: Data were collected from the Shanghai Cancer Center between January 2006 and December 2020. A total of 129 patients with RGC were included in this study, of whom 62 had carcinomas at the anastomotic site (group A) and 67 at the non-anastomotic site (group N). The clinicopathological characteristics, surgical results, recurrent diseases, and survival were investigated according to tumor location.

Results: The time interval from the previous gastrectomy to the current diagnosis was 32.0 ± 13.0 and 21.0 ± 13.4 years in groups A and N, respectively. The previous disease was benign in 51/62 cases (82.3%) in group A and 37/67 cases (55.2%) in group N (P=0.002). Thirty-three patients had documented sites of tumor recurrence through imaging or pathological examinations. The median time to recurrence was 11.0 months (range, 1.0–35.1 months). Peritoneal recurrence occurred in 11.3% (7/62) of the patients in group A versus 1.5% (1/67) of the patients in group N (P=0.006). Hepatic recurrence occurred in 3.2% (2/62) of the patients in group A versus 13.4% (9/67) of the patients in group N (P=0.038). Patients in group A had significantly better overall survival than those in group N (P=0.046).

Conclusions: The tumor location of RGC is an essential factor for predicting recurrence patterns and overall survival. When selecting an optimal postoperative follow-up program for RGC, physicians should consider recurrent features according to the tumor location.

Keywords: Gastric remnant; Gastric cancer; Recurrence; Prognosis

INTRODUCTION

Remnant gastric cancer (RGC) is a carcinoma of the remnant stomach that develops after gastrectomy, irrespective of the initial benign or malignant disease [1]. RGC treatment is one of the most challenging in clinical oncology because of the low resectability rate and necessity for concurrent resection of adjacent organs [2]. A favorable prognosis can be achieved after curative treatment [3]. With recent improvements in post-surgical follow-up programs for primary gastric cancers, the diagnosis of RGC with an operable status has

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

Author Contributions
Conceptualization: X.D.; Data curation: X.Y.; Formal analysis: C.H.; Funding acquisition: S.B.; Investigation: X.Y.; Methodology: W.J.; Project administration: C.H.; Writing - original draft: S.B.; Writing - review & editing: W.J.

increased [4]. Tumor recurrence after curative surgery is a fatal treatment complication for RGC. However, there is no relevant research describing the recurrence pattern of RGC after surgery, especially the location and time of tumor recurrence.

The tumor location of RGC is generally divided into anastomotic and non-anastomotic site [5]. The anastomotic site is where the mucosa from two different tissues heals and grows. This is also where the stapler or suture works during the first gastrectomy. The anastomotic area is stimulated by reflux of digestive juices such as bile and pancreatin [6]. Non-anastomotic tumors may originate from the accumulation of carcinogenic elements or tumor recurrence [7]. Therefore, tumor location is an essential clinicopathological feature of RGC. Previous studies have focused on the clinical significance of tumor location and have suggested that tumor location may be an important prognostic factor. Unfortunately, the effect of tumor location on recurrence has not yet been reported.

This study investigated recurrence patterns based on tumor location to address these concerns. We also examined the clinicopathological features and periprocedural complications according to the tumor location.

MATERIALS AND METHODS

Study population
This study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center. A total of 18,451 patients underwent surgical treatment for gastric cancer between January 2006 and December 2020 at Shanghai Cancer Center. We identified 212 patients with gastric cancer who had a history of partial gastrectomy. Patients who underwent distal gastrectomy more than 5 years ago were enrolled in this study. Finally, 129 patients with RGC were enrolled in this study, of whom 62 had carcinomas at the anastomotic site (group A) and 67 at the non-anastomotic site (group N).

Data collection
Data were extracted from electronic medical record system on the following study characteristics: patient demographics, initial gastrectomy, interval between the initial gastrectomy and current diagnosis for RGC, and pathological features of RGC (Lauren classification, tumor location, tumor size, depth of invasion, lymph node metastasis, lymphovascular invasion, and perineural invasion). Clinicopathological variables were categorized according to the Japanese Classification of Gastric Carcinoma (English edition ver. 3) [8]. All patients were followed-up with physical examination, blood examinations for tumor markers, chest radiography, and abdominopelvic computed tomography (CT) every three months during the first two years and every six months thereafter. Gastroscopy was performed annually. Positron emission tomography (PET)-CT and magnetic resonance imaging (MRI) was performed in cases of diagnostic doubt after the initial history and investigations. Clavien-Dindo grade IIIa or higher was defined as the presence of postoperative complications.

Tumor recurrence was confirmed by imaging or histocytology, which can include regional metastasis, distant metastasis, or anastomotic recurrence. Recurrence-free survival (RFS) was defined as the period from surgery to recurrence or last follow-up.

Statistical analysis

Comparison of clinicopathological variables between groups was performed using the Pearson χ^2 test and independent t-test for nominal scales and continuous variables, respectively. Overall survival (OS) and RFS were estimated using Kaplan-Meier survival analysis and compared using the log-rank test. Statistical significance was set at P<0.05. Statistical analyses were conducted using SPSS 22.0 statistics software (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

A patient flow diagram is shown in **Fig. 1**. A total of 129 patients with RGC were enrolled in this study. Sixty-two patients with carcinomas at the anastomotic site were classified into group A and 67 patients with carcinomas at the non-anastomotic site into group N.

Table 1 presents the baseline patient characteristics. The mean age was 64 (40–79) years in group A and 64 (35–85) years in group N (P=0.986). Females accounted for 16.1% in group A and 17.9% in group N (P=0.788). Previous disease was benign in 51/62 cases (82.3%) in group A and 37/67 patients (55.2%) in group N (P=0.001). Reconstruction methods included B-I (14.5%) and B-II (85.5%) in group A, and B-I (16.4%) and B-II (83.6%) in group N (P=0.766). The interval between the current diagnosis and previous gastrectomy was 32.0±13.0 years in group A, markedly longer than 20.0±13.4 years in group N (P=0.001). In the histopathological estimates, the tumor size was 36±21 mm and 41±25 mm in group A and N (P=0.043), respectively. The invasion depth was greater in group N than in group A (P<0.001). There was no significant difference between the groups in terms of N stage, M stage, p stage, perineural invasion, lymphovascular invasion, or perioperative treatment.

In group A, 55 (88.7%) patients underwent R0 resection and seven (11.3%) patients underwent R2 resection. Tumor bleeding or anastomotic stricture was the cause of R2
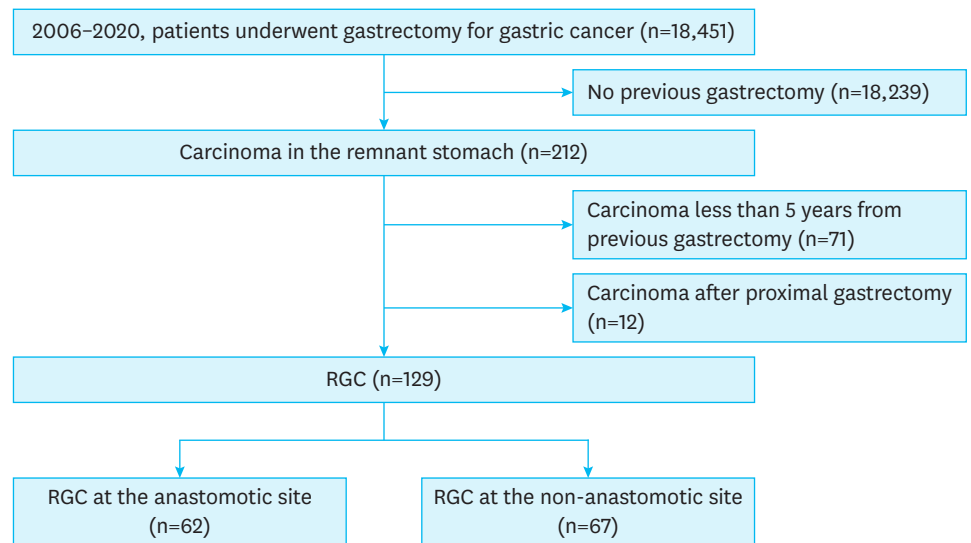
Fig. 1. Patient flow diagram.
RGC = remnant gastric cancer.

https://doi.org/10.5230/jgc.2022.22.e29

Table 1. Patient characteristics by tumor location

Characteristics	Total (n=129)	Anastomotic site (n=62)	Non-anastomotic site (n=67)	P-value
Median age (minimum, maximum) (yr)	64 (35–85)	64 (40–79)	64 (35–85)	0.986
Sex				0.788
Female	22 (17.1)	10 (16.1)	12 (17.9)	
Male	107 (82.9)	52 (83.9)	55 (82.1)	
Initial disease				0.001
Benign	88 (68.2)	51 (82.3)	37 (55.2)	
Cancer	41 (31.8)	11 (17.7)	30 (44.8)	
Initial gastrectomy				**0.766**
Billroth I	20 (15.5)	9 (14.5)	11 (16.4)	
Billroth II	109 (84.5)	53 (85.5)	56 (83.6)	
Interval (year)	30.0±13.8 (5–57)	32.0±13.0 (5–57)	21.0±13.4 (5–55)	**0.001**
Tumor size (mm)	39±23 (3–150)	36±21 (5–110)	41±25 (3–150)	**0.043**
Lauren classification				0.524
Intestinal	51 (39.5)	22 (35.5)	29 (43.3)	
Diffuse	53 (41.1)	29 (46.8)	24 (35.8)	
Mixed	20 (15.5)	8 (12.9)	12 (17.9)	
Indeterminate	5 (3.9)	3 (4.8)	2 (3.0)	
T stage				<0.001
T1	15 (11.6)	10 (16.1)	5 (7.5)	
T2	14 (10.9)	8 (12.9)	6 (9.0)	
T3	17 (13.2)	15 (24.2)	2 (3.0)	
T4	83 (64.3)	29 (46.8)	54 (80.6)	
N stage				0.335
N0	58 (45.0)	31 (50.0)	27 (40.3)	
N1	31 (24.0)	16 (25.8)	15 (22.4)	
N2	23 (17.8)	10 (16.1)	13 (19.4)	
N3	17 (13.2)	5 (8.1)	12 (17.9)	
M stage				0.621
M0	122 (94.6)	58 (93.5)	64 (95.5)	
M1	7 (5.4)	4 (6.5)	3 (4.5)	
Pathologic stage				0.165
1	25 (19.4)	15 (24.2)	10 (14.9)	
2	36 (27.9)	20 (32.3)	16 (23.9)	
3	61 (47.3)	23 (37.1)	38 (56.7)	
4	7 (5.4)	4 (6.5)	3 (4.5)	
Margin status				0.060
R0	115 (89.1)	55 (88.7)	60 (89.6)	
R1	4 (3.1)	0 (0)	4 (6.0)	
R2	10 (7.8)	7 (11.3)	3 (4.5)	
Perineural invasion				0.631
No	70 (54.3)	35 (56.5)	35 (52.2)	
Yes	59 (45.7)	27 (43.5)	32 (47.8)	
Lymphovascular invasion				0.430
No	64 (49.6)	33 (53.2)	31 (46.3)	
Yes	65 (50.4)	29 (46.8)	36 (53.7)	
Resection of adjacent organs				0.609
No	93 (72.1)	46 (74.2)	47 (70.1)	
Yes	36 (27.9)	16 (25.8)	20 (29.9)	
Perioperative treatment				0.483
No perioperative treatment	57 (44.2)	25 (40.3)	32 (47.8)	
Adjuvant	56 (43.4)	31 (50.0)	25 (37.3)	
Neoadjuvant±adjuvant	14 (10.9)	5 (8.1)	9 (13.4)	
Radiation therapy	2 (1.6)	1 (1.6)	1 (1.5)	

Values are presented as number (%) or median±standard deviations (range). Bold-faced P-values indicate statistically significant.

resection in seven patients. Among them, four had distant metastases, two had multiple palpable lymph nodes in the jejunal mesentery, and one had an unresectable lymph node invading the common hepatic artery. In group N, 60 (89.6%) patients underwent R0

Table 2. Surgical finding for RGC patients

Surgical findings	Total (n=129)	Anastomotic site (n=62)	Residual stomach (n=67)	P-value
Operation time (min)	161±45	166±47	156±43	0.224
Bleeding (mL)	185±156	169±143	200±167	0.250
Postoperative hospital stay (day)	13.5±9.5	14.7±12.5	12.4±5.4	0.183
Combined resection	36 (27.9)	16 (25.8)	20 (29.9)	0.609
Colon	19	10	9	
Liver	9	2	7	
Spleen	5	2	3	
Distal pancreas	3	2	1	
Morbidities	25 (19.4)	15 (24.2)	10 (14.9)	0.183
Intra-abdominal abscess	8	3	5	
Ileus	6	4	2	
Leakage	3	2	1	
Pleural effusion	3	2	1	
Pneumonia	2	1	1	
Intra-abdominal bleeding	1	1	0	
Lymphatic leakage	1	1	0	
Stenosis	1	1	0	
Re-operation	4 (3.1)	3 (4.8)	1 (1.5)	0.273
Operative mortality	1 (0.8)	0 (0)	1 (1.5)	

Values are presented as mean±standard deviation or number (%).
RGC = remnant gastric cancer.

resection, four (6.0%) underwent R1 resection, and three (4.5%) underwent R2 resection. Four patients who underwent R1 resection were found to have positive upper margins. Three patients with peritoneal metastasis underwent R2 resection due to tumor bleeding.

Surgical characteristics

Surgical procedures and related morbidities are shown in **Table 2**. There were no significant differences between the operation duration, amount of blood loss, and length of postoperative hospital stay.

The combined resection rates of other organs (25.8% in group A and 29.9% in group N) were comparable (P=0.609). Sixteen out of 62 patients in group A underwent combined multiple organ resection, including 10 combined colectomies, 2 specific hepatic segmental resections, 2 pancreatic body tail resections, and 2 splenectomies. Twenty out of 67 patients in group N underwent combined multiple organ resection. Among them, 9 patients underwent colectomy, 7 had specific liver segment resection, 1 had pancreatic body and tail resection, and 3 underwent splenectomy. The colon and liver are the most common joint resection organs in RGC surgery. The combined resection rate of the liver was higher in group N (2/67, 3.2%) than that in group A (7/67, 10.4%).

The rate of postoperative complications tended to be higher in group A (15/62, 24.2%) than in group N (10/67, 14.9%); however, the difference was not statistically significant. Intra-abdominal abscess (8/129) and ileus (6/129) were the most common complications after RGC surgery. Ileus occurred more often in group A (4/62 in group A vs. 2/67 in group N), whereas intra-abdominal abscess occurred more often in group N (3/62 in group A vs. 5/67 in group N). Three patients in group A (4.8%) underwent re-operation for intestinal obstruction, intestinal fistula, and abdominal bleeding, whereas one patient in group N (1.5%) underwent reoperation for ileus (P=0.273). One patient in group N died after surgery because of a severe infection caused by anastomotic leakage.

Recurrence pattern according to tumor location, initial disease, and Lauren classification

Recurrence events were established using imaging or pathological examination. **Table 3** lists the organs involved in recurrence according to tumor location. Thirty-three patients had documented sites of tumor recurrence (**Fig. 2**). Recurrence occurred most frequently in the liver (11/35), followed by the retroperitoneum (9/33) and peritoneal cavity (8/33). The recurrence rate in the peritoneum was higher in group A (7/62, 11.3%) than in group N (1/67, 1.5%; P=0.006), whereas the recurrence rate in the liver was higher in group N (9/67, 13.4%) than in group A (2/62, 3.2%; P=0.038). Recurrence rate in the retroperitoneum was higher in group N (6/67, 9.0%) than in group A (3/62, 4.8%), although the difference was not significant (P=0.359). Distant recurrences were observed in lung (2/67, 3.0%) and bone (1/67, 1.5%) in group N. Recurrences at the anastomotic site were observed in 2 out of 62 (3.2%) patients in group A.

Considering the significant difference in the distribution of the initial disease between the groups, we analyzed the relationship between the recurrence pattern and initial disease in RGC (**Table 3**). Patients with an initial malignant disease had a significantly higher proportion of tumor recurrence (15/41) than those with an initial benign disease (18/88; P=0.017); however, the characteristics of the initial disease were not significantly associated with the site of tumor recurrence.

We analyzed the recurrence pattern in relation to the Lauren classification of RGC (**Table 3**) because it is essential for predicting recurrence patterns in gastric cancer [9]. There was no significant correlation between recurrence pattern and histological type. In summary, the initial disease may affect the recurrence rate of RGC, and tumor location may affect the recurrence site.

Survival outcomes

The median follow-up was 18.0 months (range, 3–144 months). Median RFS and median OS were 12.0 and 16.8 months, respectively (**Table 4**). Group A showed a longer RFS than group N, although the difference was not statistically significant (P=0.076). Demographic features, including tumor size, pathological stage, T stage, N stage, and lymphovascular invasion, predicted significantly shorter RFS in univariate analysis (**Fig. 3**). The independent predictors of RFS were tumor size (hazard ratio [HR], 2.12; 95% confidence interval [CI], 1.12–4.01; P=0.021) and lymphovascular invasion (HR, 3.79; 95% CI, 1.95–7.37; P=0.002). Tumor location, tumor size, pathological stage, T stage, N stage, and lymphovascular invasion were significantly associated with a shorter OS (**Fig. 3**). On multivariate analysis, pathological stage was an independent predictor of OS (HR, 2.78; 95% CI, 1.37–5.64; P=0.005).

Table 3. Recurrence pattern of RGC

Variables	Tumor location				Initial disease				Lauren classification			
	Total (n=129)	Anastomotic site (n=62)	Residual stomach (n=67)	P-value	Total (n=129)	Benign (n=88)	Malignant (n=41)	P-value	Total (n=124)	Intestinal type (n=51)	Diffuse/Mixed type (n=73)	P-value
No. of involved organs	33 (25.6)	14 (22.6)	19 (28.4)	0.452	33 (25.6)	18 (20.5)	15 (36.6)	0.017	33 (26.6)	14 (27.5)	19 (26.0)	0.140
Peritoneal cavity	8	7	1	0.006	8	7	1	0.773	8	4	4	0.402
Liver	11	2	9	0.038	11	5	6	0.910	11	6	5	0.303
Retroperitoneum	9	3	6	0.359	9	4	5	0.888	9	2	7	0.767
Lung	2	0	2	0.170	2	1	1	0.423	2	2	0	0.912
Bone	1	0	1	0.334	1	0	1	0.859	1	0	1	0.599
Recurrence at the anastomosis	2	2	0	0.138	2	1	1	0.423	2	0	2	0.767

RGC = remnant gastric cancer.
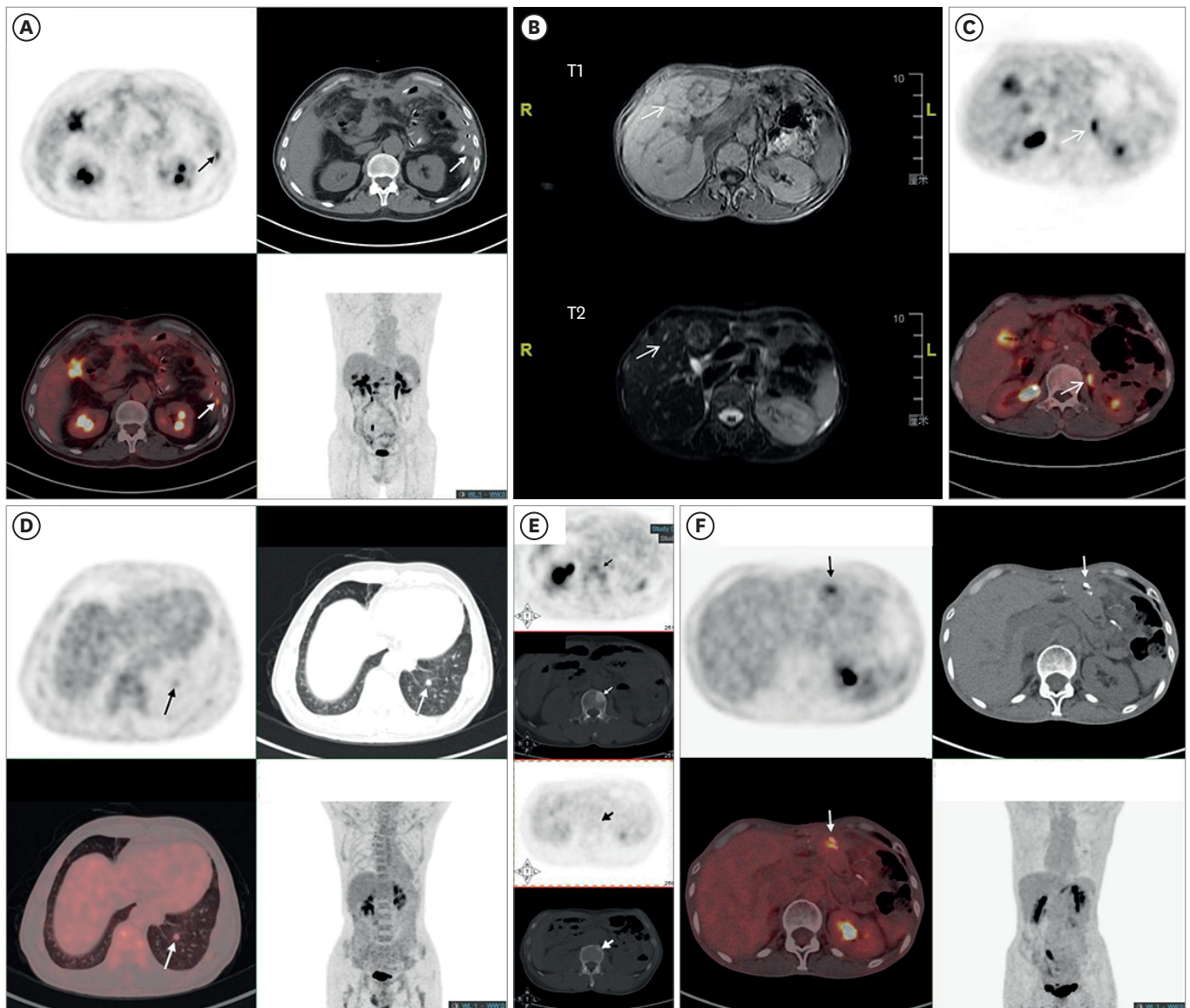
Fig. 2. Representative recurrence after gastrectomy for RGC. (A) Recurrence in peritoneal cavity detected by PET-CT scan in a 66-year-old man with pT3N0M0 RGC at 3 months after radical total gastectomy. (B) Liver metastasis detected by MRI in a 58-year-old woman with pT4aN2M0 RGC at 9 months after radical total gastectomy. (C) Recurrence in retroperitoneum detected by PET-CT scan in a 62-year-old man with pT2N1M0 RGC at 21 months after radical total gastectomy. (D) Lung metastasis detected by PET-CT scan in a 72-year-old man with pT2N0M0 RGC 32 months after surgery. (E) Bone metastasis detected by PET-CT scan in a 56-year-old man with pT4aN3M0 at 27 months after radical total gastectomy. (F) Recurrence at the anastomosis of the transverse colon detected by PET-CT scan in a 46-year-old man with pT4bN0M0 at 25 months after radical total gastectomy.
RGC = remnant gastric cancer; PET-CT = positron emission tomography-computed tomography; MRI = magnetic resonance imaging.

DISCUSSION

Our findings suggest that tumor location is a significant predictor of recurrence patterns and OS. Recurrence of anastomotic RGC occurs mainly in the peritoneal cavity, whereas non-anastomotic RGC often recur in the liver, the retroperitoneal space, and distant organs.

The interval between the initial gastrectomy and RGC diagnosis differs across studies. Previous studies have shown that the interval time for RGC with initial malignant disease

Table 4. Univariate and multivariate analysis for OS and RFS

Category	Predictor	RFS				OS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	<64 years	1	0.589			1	0.646		
	≥64 years	1.17 (0.67–2.04)				1.16 (0.61–2.20)			
Sex	Male	1	0.055			1	0.160		
	Female	1.90 (0.99–3.65)				1.71 (0.81–3.64)			
Tumor location	Anastomotic site	1	0.080			1	0.046		
	Non-anastomotic site	1.68 (0.94–2.99)				2.09 (1.01–4.32)			
Tumor size	<30 mm	1	0.008	1	0.021	1	0.011		
	≥30 mm	2.36 (1.25–4.45)		2.12 (1.12–4.01)		2.75 (1.26–6.00)			
Lauren classification	Intestinal	1				1			
	Diffuse or Mixed	1.30 (0.73–2.31)	0.379			1.84 (0.89–3.78)	0.099		
Pathological stage	Stage 1–2	1	0.004			1	0.003	1	0.005
	Stage 3	2.30 (1.30–4.07)				2.94 (1.46–5.94)		2.78 (1.37–5.64)	
T stage	T1–T3	1	0.091			1	0.007		
	T4	1.66 (0.92–3.01)				3.30 (1.38–7.90)			
N stage	N0	1	0.003			1	0.038		
	N1–3	2.45 (1.34–4.35)				2.07 (1.04–4.10)			
Lymphovascular invasion	No	1	0.001	1	0.002	1	0.014		
	Yes	2.63 (1.45–4.76)		2.52 (1.39–4.58)		2.32 (1.19–4.54)			
Perineural invasion	No	1	0.251			1	0.399		
	Yes	1.39 (0.79–2.44)				1.32 (0.69–2.52)			
CEA >5 ng/mL	No	1	0.153			1			
	Yes	1.69 (0.82–3.49)				1.39 (0.58–3.34)	0.458		

OS = overall survival; RFS = recurrence-free survival; HR = hazard ratio; CI = confidence interval; CEA = carcinoembryonic antigen.

is shorter than those with initial benign disease [10,11]. In our study, the interval time for RGC at the anastomotic site was longer than that for RGC at the residual area. The difference in interval time suggests that different mechanisms are associated with RGC development at different locations. The mainstream view is that regurgitation of digestive juices, especially bile and pancreatic juice, is a carcinogenic stimulation at the anastomotic site [6,12]. In contrast, RGC at the residual location may occur in mucosa with a high risk of carcinogenesis, such as atrophic changes and intestinal metaplasia [7].

In this study, anastomotic and non-anastomotic tumors showed significant differences in terms of tumor depth and size. Non-anastomotic tumors had a significantly higher T stage than anastomotic tumors. Non-anastomotic tumors had higher N and Tumor, Node, Metastasis (TNM) stages, although the difference was not statistically significant. Symptoms of anastomotic tumors appear earlier and more frequently, thus allowing for earlier diagnosis. This may account for the difference between anastomotic and non-anastomotic tumors.

The main takeaway from this study was that the recurrence pattern of RGC varies depending on the tumor location. We described different recurrence methods at the anastomotic and non-anastomotic sites. Anastomotic tumors are prone to recurrence in the peritoneal cavity and anastomotic stomas. RGC at the residual site are prone to recurrence in the retroperitoneum, liver, lung, and bone. The most common metastatic organs among patients with gastric cancer include the liver, peritoneum, lungs, and bones. Recurrence of gastric cancer is divided into local, regional, and adjacent organs, and distant metastasis. Most recurrences occur within 2–2.5 years following surgical excision [13]. Extragastric recurrence may be an essential factor leading to poor prognosis in gastric cancer [14]. Two different hypotheses have been widely accepted to explain the mechanism of gastric cancer metastasis. The classical "seed and soil" hypothesis posits that the organ distribution of
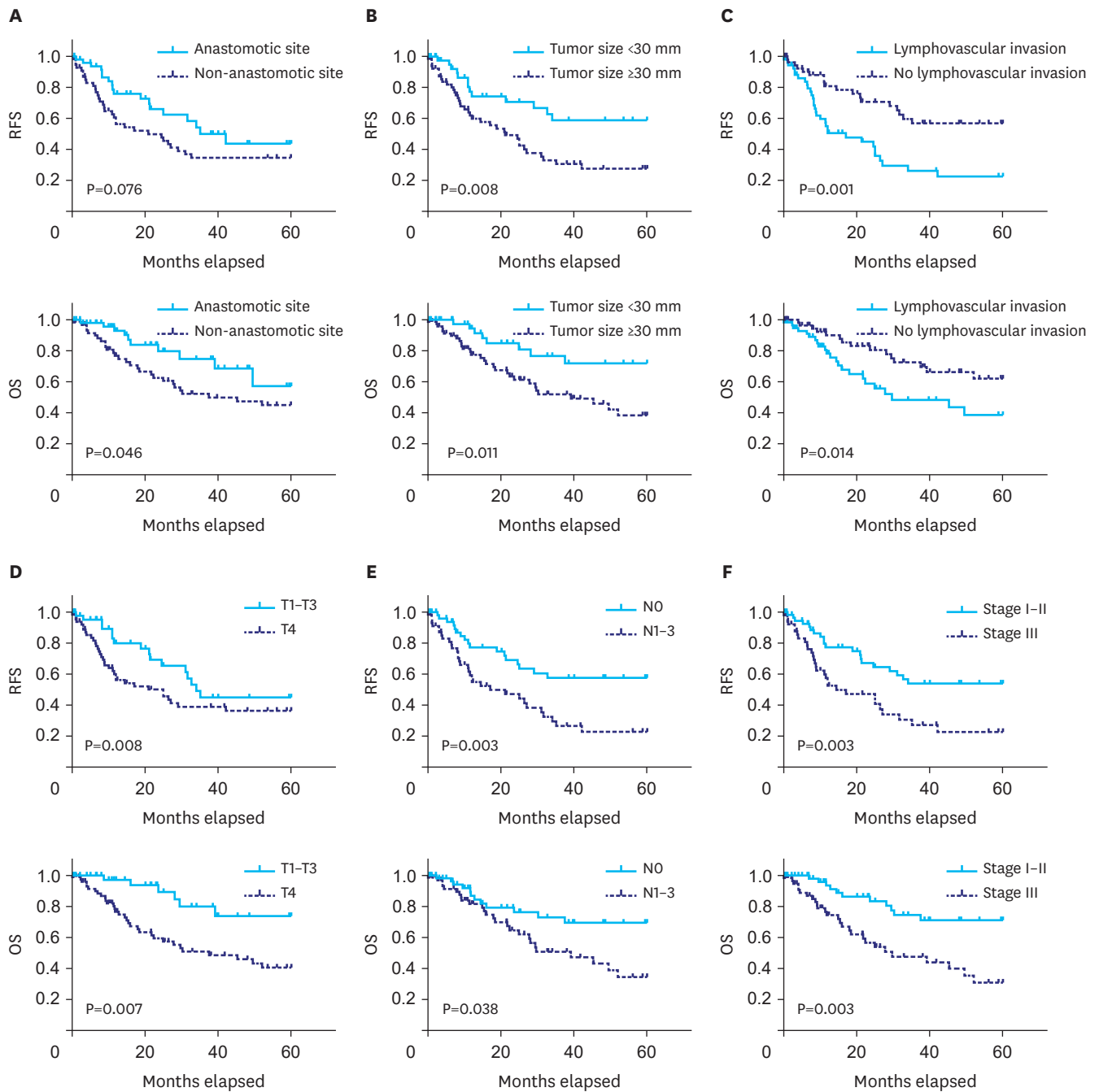
Fig. 3. Kaplan-Meier estimates of RFS and OS according to tumor location (A), tumor size (B), T stage (C), N stage (D), pathological stage (E), and lymphovascular invasion (F).
RFS = relapse-free survival; OS = overall survival.

metastases produced by certain tumor cells has a specific affinity for the milieu of certain organs [15]. The "anatomical/mechanical" hypothesis implies the typical spreading based on the anatomical factors [16]. Previous studies have indicated that the metastatic pattern of cardiac cancer is entirely different from that of noncardiac cancers [17]. Cardiac cancer often metastasizes to the lungs and bones, and less to the peritoneal cavity. The metastasis of cardiac cancer to the lung conforms to the anatomical/mechanical theory because blood flows directly to the lung from the proximal ventricle. The metastasis of cardiac cancer is

more frequent in the liver than in non-cardiac cancer, indicating a biological difference in line with the "seed and soil" hypothesis. Our results showed that RGC at the non-anastomotic location recurred after surgery, similar to cardiac carcinoma. In contrast, the recurrence pattern of anastomotic tumors is similar to those of gastric corpus carcinoma and gastric antral carcinoma. To our knowledge, this is the first study to evaluate site-specific tumor recurrence in RGC.

The recurrence pattern has been reported to vary significantly according to Lauren classification [9,18]. For intestinal-type gastric cancer, distant metastasis is the most common site, followed by locoregional and peritoneal metastases. The most common recurrence site for diffuse/mixed-type gastric cancer is the peritoneum, followed by distant and locoregional sites. In this study, no significant correlation was observed between the recurrence pattern and histological type of RGC. Environmental features and disease characteristics may influence the recurrence pattern accordingly. Adhesions around the gastric stump spatially block peritoneal dissemination of tumor cells [19]. In addition, adhesion after initial surgery works as a complicated combination of cytokines, growth factors, and components produced by platelets, macrophages, and other cells at the molecular level [20]. Intraperitoneal adhesions may alter the peritoneal microenvironment, thereby interfering with tumor cell colonization. Previous studies have shown that the likelihood of peritoneal metastasis in proximal gastric cancer is lower than that in distal gastric cancer [17]. Most RGCs are tumors of the proximal stomach after distal gastrectomy, minimizing the risk of peritoneal recurrence. Furthermore, the statistical strength of this conclusion was limited by the sample size. Further studies with larger sample sizes are required to confirm this conclusion.

Lymphovascular invasion was defined as the presence of tumor emboli in the lymphatic channels or vascular lumens [21]. This is the primary and essential step in the systemic dissemination of cancer cells [22]. Lymphovascular invasion is an independent risk factor for lymph node metastasis [23]. It has been documented as a poor prognostic factor for many solid organ tumors [24]. Some of these malignancies were included in the American Joint Committee on Cancer TNM staging criteria, in which the patient's presence is upstaged. Lymphovascular invasion was observed in 51.2% of the patients with RGC in this study. It is an independent prognostic factor affecting OS and RFS in patients with RGC. We recommend that the lymphovascular invasion status be considered for RGC treatment stratification.

This study had several limitations. Given the retrospective nature of this study, there was an inherent risk of bias. However, we believe that the findings of this study appear promising given that the number of eliminated patients with missing data was less than 10% of the research population. The duration of follow-up was short. Further long-term follow-up studies are required to confirm our results. The present study presents a different pattern of tumor progression at different tumor locations in RGC. The underlying molecular mechanism of tumor development and progression based on tumor location is not clear; thus, further investigations are required to better understand the role of tumor location in predicting tumor progression in RGC.

In summary, the findings of this study provide some insightful clues regarding the relationship between tumor location and recurrence characteristics, which might assist in predicting the prognosis of RGC patients. Individualized management strategies should be implemented according to the recurrence patterns of RGC at different tumor locations.

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