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Prognosis and clinicopathologic features in patients with gastric stump cancer after curative surgery

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ABSTRACT

Background Gastric stump ("remnant") cancer is the development of a malignancy related to previous gastric surgery. Prognosis in gastric stump cancer, compared with that in primary gastric cancer, is still controversial.

Methods From January 1988 to December 2012 at a single medical centre in Taiwan, 105 patients with gastric stump cancer, including 85 with previous peptic ulcer disease and 20 with previous gastric cancer, were analyzed for clinicopathologic characteristics and overall survival (OS).

Results The 5-year OS rates for patients with gastric stump cancer and with primary gastric cancer were 51.2% and 54.5% respectively ($p = 0.035$). Analysis of clinicopathologic characteristics indicated that, compared with patients having primary gastric cancer, those with gastric stump cancer had more lymph node metastasis ($p < 0.001$) and had been diagnosed at a more advanced stage ($p = 0.047$). Multivariate analysis with OS as an endpoint showed that age [$p = 0.015$; hazard ratio (HR): 2.300; 95% confidence interval (CI): 1.173 to 4.509], tumour size ($p = 0.037$; HR: 1.700; 95% CI: 1.031 to 2.801), stromal reaction ($p = 0.021$; HR: 1.802; 95% CI: 1.094 to 2.969), and pathologic N category ($p = 0.001$; HR: 1.449; 95% CI: 1.161 to 1.807) were independent predictors in gastric stump cancer. The OS rates for patients with gastric stump cancer who previously had gastric cancer or peptic ulcer disease were 72.9% and 50.0% respectively ($p = 0.019$). The Borrmann classification was more superficial ($p = 0.005$), lymph node metastases were fewer ($p = 0.004$), and staging was less advanced ($p = 0.025$) in patients with gastric stump cancer who previously had gastric cancer than in their counterparts who previously had peptic ulcer disease.

Conclusions Survival is poorer in patients with gastric stump cancer who previously had peptic ulcer disease than in those who previously had primary gastric cancer. Patients with gastric stump cancer who previously had gastric cancer and could receive curative gastrectomy tended to have a better prognosis because of a more superficial Borrmann classification. Regular follow-up in patients who have undergone gastric surgery is recommended for the early detection of gastric stump cancer.

Key Words Gastric remnant cancer, gastric stump cancer, peptic ulcers, gastrectomy

INTRODUCTION

Gastric cancer is a common malignancy in the upper gastrointestinal tract. It is currently the 3rd leading cause of cancer-related deaths worldwide[1]. The treatment for gastric cancer is surgical resection, with curative intent for patients without distant metastasis. Extended regional D2 lymph node dissection is a standard procedure in gastric cancer surgery[2]. The incidence of gastric cancer has been declining in recent decades, but the incidence of gastric stump cancer is increasing because of prior peptic ulcer surgery and a long latency period[3–6].

Gastric stump ("remnant") cancer is defined as a malignancy occurring in the gastric stump at least 5 years after

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gastrectomy. The development of the malignancy is associated with prior gastric surgery, including procedures for peptic ulcer disease or previous gastric cancer. Because of reconstruction of the gastrointestinal tract after gastrectomy, including Billroth I and Billroth II procedures, the gastric stump is affected by reflux of bile acids, resulting in gastritis and further intestinal metaplasia and dysplasia of the gastric mucosa. Those alterations eventually develop and transform into gastric carcinoma. Moreover, gastric stump cancer is typically found to be a more advanced gastric cancer associated with a relatively lower curative resection rate[7,8]. However, the clinicopathologic characteristics and prognosis for gastric stump cancer, compared with those for primary gastric cancer, are still controversial. In the present study, we investigated the clinicopathologic characteristics and prognosis in gastric stump cancer and evaluated differences between patients who previously had benign peptic ulcer disease and those who had gastric cancer.

METHODS

In this retrospective study, the charts of 126 patients with gastric stump cancer who underwent gastrectomy from January 1998 to December 2012 at the Department of Surgery in Taipei Veterans General Hospital, Taiwan, were reviewed. Of those patients, 105 received curative resection, and 21 received palliative surgery. Of the 105 patients treated curatively, 85 had previously undergone gastrectomy because of peptic ulcer disease, and 20, because of previous gastric cancer (Figure 1). During the study period, 2622 patients with primary gastric cancer who received curative surgery were enrolled for comparison with the patients who had gastric stump cancer.

Before their operation, all patients underwent upper gastrointestinal endoscopy, chest radiography, and either or both of abdominal sonography and abdominal computed tomography for clinical tumour staging. Patients who could not undergo curative surgery—those receiving palliative resection and those with unresectable tumours, peritoneal carcinomatosis, or distant metastases (bone, lung, liver)—were excluded from the study. Patients whose pathology report showed other than adenocarcinoma were also excluded.

Radical total gastrectomy was performed for proximal-third lesions, and radical subtotal gastrectomy was performed for distal- or middle-third lesions. At least D1+α lymph node dissection was performed for early gastric cancer, and a D2 lymph node dissection was performed for

FIGURE 1 Clinical profile of patients with gastric stump cancer.

advanced gastric cancer. Basic demographic and clinical data for the patients were collected, including age, sex, tumour location, tumour size, gross appearance, histology analyses, lymph node metastasis status, and pathologic stage.

Gross features of the specimens were based on tumour size, tumour location, and Borrmann classification. The Borrmann classifications were superficial type, Borrmann type I (polypoid tumour), Borrmann type II (ulcerated tumour with sharply demarcated margin), Borrmann type III (ulcerated tumour without a demarcated margin and infiltrating to surrounding gastric wall), and Borrmann type IV (diffuse infiltrating tumour). Borrmann types I and II are well-defined tumours (localized type); Borrmann types III and IV are ill-defined tumours (infiltrating type). The microscopic features—histology, pathology, and cell differentiation—were analyzed by cell grading for tumour differentiation, stromal reaction type (medullary, intermediate, or scirrhous), Lauren histologic classification (intestinal or diffuse), Ming histologic classification[9] (expanding or infiltrating), and lymphovascular invasion patterns. The staging system used was the TNM system[10].

After surgery, patients were followed at the outpatient clinic every 3 months for at least the first 5 years after gastrectomy, and every 6 months thereafter (patients not experiencing disease relapse or recurrence for more than 5 years). Before 2008, adjuvant chemotherapy or radiotherapy, or both, were not routinely performed after curative surgery, but were provided to patients with gastric cancer at the time of tumour recurrence. After 2008, the adjuvant oral fluoropyrimidine S-1 was prescribed in our hospital, if the patient found it financially affordable, for stage II or III gastric cancer after curative resection.

Recurrence was defined as first evidence of tumour relapse in imaging, in cytology analysis of ascites from an abdominal tap, in endoscopy findings, or in bone scans. The relapse pattern was recorded in detail. Follow-up data were prospectively collected and regularly updated. Survival in patients with gastric cancer was followed for more than 10 years. Overall survival was defined as the period from the date of surgery to the date of death or last follow-up. Disease-free survival was defined as the period from the date of surgery for gastric cancer during which the patient survived without recurrence.

The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB-TPEVGH no. 2018-06-005BC).

All statistical analyses were carried out using the IBM SPSS Statistics software application (version 19.0: IBM, Armonk, NY, U.S.A.). Clinicopathologic differences were compared using the chi-square test. Survival was evaluated using Kaplan–Meier analysis with log-rank test. Prognostic factors such as age, sex, tumour size, Borrmann classification, cell grade, Lauren histology, stromal reaction, lymphovascular invasion, and T and N stage were evaluated in a Cox regression model with OS as an endpoint. A *p* value less than 0.05 was considered statistically significant.

RESULTS

The R0 resection rate in gastric stump cancer was 83.3%; in primary gastric cancer, it was 87.8%. The mean age of
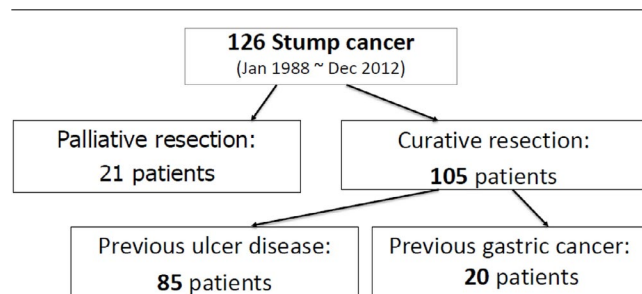
patients with gastric stump cancer (69.4 ± 10.0 years) was greater than that of patients with primary gastric cancer (66.6 ± 12.6 years, $p = 0.036$). The male:female ratio was also greater in patients with gastric stump cancer than in those with primary gastric cancer, $p = 0.004$. Analysis of clinicopathologic characteristics indicates that, compared with their counterparts having primary gastric cancer, patients with gastric stump cancer had more lymph node metastasis ($p < 0.001$) and were diagnosed at a more advanced stage ($p = 0.047$, Table I).

The 5-year OS rates for patients with gastric stump cancer and with primary gastric cancer were 51.2% and 54.5% respectively ($p = 0.035$). The 5-year disease-free survival rates of patients with gastric stump cancer and with primary gastric cancer were 46.2% and 54.1% respectively ($p = 0.043$, Figure 2).

Multivariate analysis with OS as an endpoint showed that age [$p = 0.015$; hazard ratio (HR): 2.300; 95% confidence interval (CI): 1.173 to 4.509], tumour size ($p = 0.037$; HR: 1.700; 95% CI: 1.031 to 2.801), stromal reaction ($p = 0.021$; HR: 1.802; 95% CI: 1.094 to 2.969), and pathologic N stage ($p = 0.001$; HR: 1.449; 95% CI: 1.161 to 1.807) were independent predictors in gastric stump cancer (Table II).

The median latency period for the 105 patients with gastric stump cancer was 25.7 years. It was significantly longer for patients who previously had peptic ulcer disease than for those who previously had gastric cancer (27.3 years vs. 11.8 years, $p < 0.001$). With respect to the anastomosis procedure in patients with gastric stump cancer, Billroth I anastomoses had been created in 5 patients with previous peptic ulcer disease and in 6 with previous gastric cancer; Billroth II anastomoses had been created in 80 and 14 patients respectively ($p = 0.002$). We found that 16 of the 94 patients with Billroth II anastomoses had mesentery lymph node metastases, for a positive rate of 17.0%. In comparing the clinicopathologic features of the groups with a prior gastric cancer history and with a prior peptic ulcer disease history, the Borrmann classification was more superficial ($p = 0.005$), lymph node metastases were fewer ($p = 0.004$), and staging was less advanced ($p = 0.025$) in patients with a prior gastric cancer history (Table III). The 5-year OS was poorer in patients with gastric stump cancer after prior peptic ulcer disease than in those after prior gastric cancer ($p = 0.019$, Figure 3).

DISCUSSION

Although the incidence of gastric cancer has declined in recent decades, the prevalence of gastric stump cancer has not yet declined because of the long latency after prior gastric surgery. Our results show that, compared with patients having primary gastric cancer, those with gastric stump cancer have more lymph node metastasis and are diagnosed at a more advanced stage. The prognosis in gastric stump cancer is also poorer than that in primary gastric cancer. Because of the long latency after prior gastric surgery, gastric stump cancer will remain an important medical issue in the coming decades.

Compared with patients whose gastric stump cancer was related to prior peptic ulcer disease, those whose gastric stump cancer was related to a prior gastric cancer history

TABLE I   Clinical profiles of patients with gastric stump cancer and with primary gastric cancer

Variable	Patient group		*p* Value[a]
	Gastric stump cancer	Primary gastric cancer	
Patients *(n)*	105	2622	
Mean age (years)	68.9±9.6	66.6±12.6	**0.036**
Sex [n (%)]			
Men	91 (86.7)	1952 (74.4)	
Women	14 (13.3)	672 (25.6)	**0.004**
Tumour size group [*n* (%)]			
<4 cm	50 (47.6)	1135 (43.3)	
4–8 cm	42 (40.0)	1131 (43.1)	
>8 cm	13 (12.4)	356 (13.6)	0.679
Differentiation [*n* (%)]			
Poorly differentiated	48 (45.7)	1375 (52.4)	
Moderately differentiated	54 (51.4)	1177 (44.9)	
Well differentiated	3 (2.9)	70 (2.7)	0.398
Gross appearance [*n* (%)]			
Superficial	41 (39.0)	979 (37.3)	
Borrmann type I–II	22 (21.0)	518 (19.8)	
Borrmann type III–IV	42 (40.0)	1125 (42.9)	0.839
Stromal reaction type [*n* (%)]			
Medullary	31 (29.5)	698 (26.6)	
Intermediate	55 (52.4)	1286 (49.1)	
Scirrhous	19 (18.1)	638 (24.3)	0.337
Lauren histology [*n* (%)]			
Intestinal type	66 (62.9)	1507 (57.5)	
Diffuse type	39 (37.1)	1115 (42.5)	0.274
Ming histology [*n* (%)]			
Expanding	33 (31.4)	806 (30.7)	
Infiltrating	72 (68.6)	1816 (69.3)	0.881
Lymphovascular invasion [*n* (%)]			
No	39 (37.1)	1117 (42.6)	
Yes	66 (62.9)	1505 (57.4)	0.267
Pathologic T stage [*n* (%)]			
T1	40 (38.1)	922 (35.2)	
T2	18 (17.1)	390 (14.9)	
T3	28 (26.7)	684 (26.1)	
T4	19 (18.1)	626 (23.9)	0.566
Pathologic N stage [*n* (%)]			
N0	34 (32.4)	1262 (48.1)	
N1	22 (21.0)	465 (17.7)	
N2	27 (25.7)	327 (12.5)	
N3	22 (20.9)	568 (21.7)	**<0.001**
TNM stage[b] [*n* (%)]			
I	39 (37.1)	1250 (47.7)	
II	22 (21.0)	556 (21.2)	
III	44 (41.9)	816 (31.1)	**0.047**
5-Year OS rate (%)	51.2	54.5	**0.035**
5-Year DFS rate (%)	46.2	54.1	**0.043**

[a]   Significant values are shown in boldface type.
[b]   According to the American Joint Committee on Cancer staging manual, 8th edition.
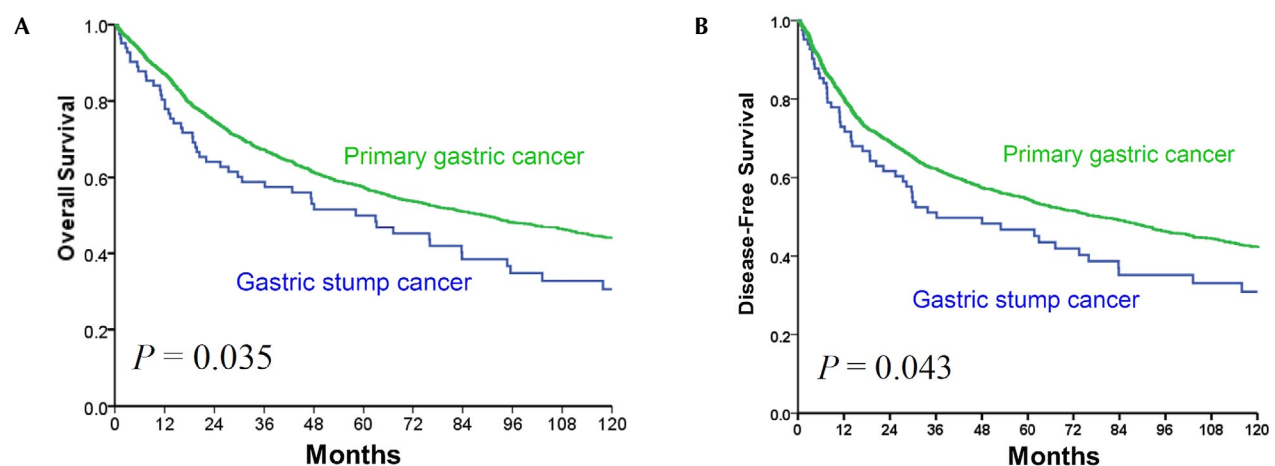OS = overall survival; DFS = disease-free survival.

FIGURE 2   (A) Overall survival (months) for patients with gastric stump cancer and for those with primary gastric cancer (log-rank $p = 0.035$). (B) Disease-free survival (months) for patients with gastric stump cancer and for those with primary gastric cancer (log-rank $p = 0.043$).

TABLE II   Multivariate analysis with overall survival as an endpoint, 105 patients with gastric stump cancer

Variable	Analysis		
	p Value[a]	HR	95% CI
Age	**0.015**	2.300	1.173 to 4.509
Sex	0.309	1.612	0.642 to 4.045
Tumour size	**0.037**	1.700	1.031 to 2.801
Borrmann classification	0.547	0.883	0.590 to 1.323
Differentiation	0.867	1.077	0.452 to 2.564
Lauren histology	0.308	0.569	0.193 to 1.680
Stromal reaction	**0.021**	1.802	1.094 to 2.969
Lymphovascular invasion	0.901	1.056	0.448 to 2.489
Pathologic T stage[b]	0.451	1.157	0.792 to 1.697
Pathologic N stage[b]	**0.001**	1.449	1.161 to 1.807

[a] Significant values are shown in boldface type.
[b] According to the American Joint Committee on Cancer staging manual, 8th edition.
HR = hazard ratio; CI = confidence interval.

had a relatively better prognosis. Ahn *et al.*[11] reported that the difference in OS between patients who previously had a benign disease and those who had a previous cancer was nonsignificant. However, Hu *et al.*[12] reported that prognosis was better for patients with gastric stump cancer after prior benign disease than for their counterparts after a prior gastric cancer. In contrast, our study showed that prognosis was relatively better for patients with gastric stump cancer after a prior history of gastric cancer than after a prior history of benign peptic ulcer disease. Because patients with gastric remnant cancer after a prior history of gastric cancer were regularly followed at our outpatient clinic and regularly received upper gastrointestinal endoscopy, abdominal sonography, or abdominal computed tomography, recurrent tumours at the gastric remnant could be detected early. Patients with a prior history of benign peptic

ulcer disease have a longer latency period to gastric stump cancer after gastrectomy for ulcer disease. Because of that long latency period, those patients did not receive regular follow-up at our clinic. Hence, their stump cancer was not detected early in its development. They were diagnosed when symptoms such as obstruction or tumour bleeding developed. Prognosis is therefore relatively poorer for patients with peptic ulcer–related gastric stump cancer than for those whose stump recurrence was related to gastric cancer. It is very important that regular upper gastrointestinal endoscopy be performed for patients who have undergone gastric surgery for peptic ulcer disease.

Some researchers have compared the prognosis in gastric stump cancer with that in gastric cancer in the high body or cardia regions[13–16]. In our study, the 5-year OS and disease-free survival rates for primary cardia or high-body gastric cancer compared with gastric stump cancer were, respectively, 55.6% and 51.2% ($p = 0.057$) and 52.3% and 46.2% ($p = 0.069$). Although we observed a trend in our series toward a poorer prognosis for patients with gastric stump cancer, the differences were not statistically significant. To the best of our knowledge, the anatomic structure of gastric stump cancer is, because of previous gastric surgery, quite different from that of primary gastric cancer in the cardia or high-body regions. In addition, most gastric stump cancers develop around the anastomotic site of the gastroduodenostomy in Billroth I reconstructions and of the gastrojejunostomy in Billroth II reconstructions[17]. The development of gastric stump cancer might be associated with reflux of bile and pancreas secretions, resulting in inflammation and degeneration of the gastric mucosa. Because of persistent gastritis and atrophic gastritis, the gastric mucosa develops intestinal metaplasia and dysplasia, which eventually transforms into gastric adenocarcinoma. The environment of the gastric remnant is quite different from that of the natural anatomic structure of gastric cancer in the high-body and cardia regions.

In the literature, the resectability of gastric stump cancer ranges from 71% to 94%. The R0 resection rate in gastric stump cancer ranges from 77% to 85%[3]. The rates of resectability and R0 resection in gastric stump cancer are

TABLE III   Clinical profile of patients with gastric stump cancer and prior ulcer disease or prior gastric cancer

Variable	Patient group		*p* Value[a]
	Prior ulcer disease	Prior gastric cancer	
Patients *(n)*	85	20	
Mean age (years)	69.4±10.0	66.5±8.9	0.239
Incubation period (years)	27.3	11.8	**<0.001**
Reconstruction method [*n* (%)]			
B-I anastomosis	5 (5.9)	6 (30)	
B-II anastomosis	80 (94.1)	14 (70)	**0.002**
Sex [*n* (%)]			
Men	75 (88.2)	16 (80)	
Women	10 (11.8)	4 (20)	0.330
Tumour size group [*n* (%)]			
<4 cm	37 (43.5)	13 (65)	
4–8 cm	36 (42.4)	6 (30)	
>8 cm	12 (14.1)	1 (5)	0.195
Differentiation [*n* (%)]			
Poorly differentiated	39 (46.0)	9 (45)	
Moderately differentiated	45 (52.9)	9 (45)	
Well differentiated	1 (1.1)	2 (10)	0.100
Gross appearance [*n* (%)]			
Superficial type	27 (31.8)	14 (70)	
Borrmann type I–II	21 (24.7)	1 (5)	
Borrmann type III–IV	37 (43.5)	5 (25)	**0.005**
Stromal reaction type [*n* (%)]			
Medullary	22 (25.9)	9 (45)	
Intermediate	47 (55.3)	8 (40)	
Scirrhous	16 (18.8)	3 (15)	0.240
Lauren histology [*n* (%)]			
Intestinal type	53 (62.4)	13 (65)	
Diffuse type	32 (37.6)	7 (35)	0.826
Ming histology [*n* (%)]			
Expanding	25 (29.4)	8 (40)	
Infiltrating	60 (70.6)	12 (60)	0.359
Lymphovascular invasion [*n* (%)]			
No	28 (32.9)	11 (55)	
Yes	57 (67.1)	9 (45)	0.066
Pathologic T stage [*n* (%)]			
T1	28 (32.9)	12 (60)	
T2	16 (18.8)	2 (10)	
T3	23 (27.1)	5 (25)	
T4	18 (21.2)	1 (5)	0.102
Pathologic N stage [*n* (%)]			
N0	23 (27.1)	11 (55)	
N1	15 (17.6)	7 (35)	
N2	26 (30.6)	1 (5)	
N3	21 (24.7)	1 (5)	**0.004**

TABLE III   Continued

Variable	Patient group		*p* Value[a]
	Prior ulcer disease	Prior gastric cancer	
TNM stage [*n* (%)]			
I	28 (33.0)	11 (55)	
II	16 (18.8)	6 (30)	
III	41 (48.2)	3 (15)	**0.025**
5-Year OS rate (%)	50	72.9	**0.019**
5-Year DFS rate (%)	46.7	45.7	0.953

[a]   Significant values are shown in boldface type.
[b]   According to the American Joint Committee on Cancer staging manual, 8th edition.
OS = overall survival; DFS = disease-free survival.

lower than those in primary proximal-third gastric cancer. In our series, the R0 resection rate in gastric stump cancer was 83.3%; for primary gastric cancer, it was 87.8%. In multivariate analysis, larger tumour size and greater stromal reaction were independent predictors for gastric stump cancer. Surgeons are therefore challenged in attempting curative resection for very advanced gastric stump cancer.

Lymph node metastasis plays an important role in gastric cancer. It is also an important prognostic factor in gastric stump cancer. The main lymphatic drainage pathway is usually along the gastric cardia region, the left gastric artery, and the splenic artery. Radical lymph node dissection is therefore still necessary, as recommended by the Japanese Gastric Cancer Association[18]. In addition, a previous publication reported that the drainage pathway for lymph node metastasis is along the anastomotic site of the jejunum[19]. In our cohort, 16 of 94 patients (17.0%) had mesentery lymph node metastases after Billroth II anastomotic procedures. Resection of the jejunal mesentery near the anastomotic site is therefore still recommended in patients who receive a Billroth II anastomosis.

Our study reports on a 25-year experience in a single centre, based on a retrospective investigation. We collected data from patients with gastric cancer who underwent curative resection and who had complete pathology examinations and follow-up survival data. Selection bias might have be a factor in this retrospective cohort study. We focused on the clinicopathologic characteristics and clinical outcomes of patients with gastric stump cancer.

CONCLUSIONS

Survival was poorer in patients with gastric stump cancer than in patients with primary gastric cancer. Because of a more superficial Borrmann classification, prognosis tended to be better in patients with gastric stump cancer who previously had gastric cancer treated with curative gastrectomy. Regular follow-up in patients who have previously undergone gastric surgery is recommended for the early detection of gastric stump cancer. Further studies are necessary to evaluate environmental alterations in the gastric remnant and tumour behaviour in gastric stump cancer.
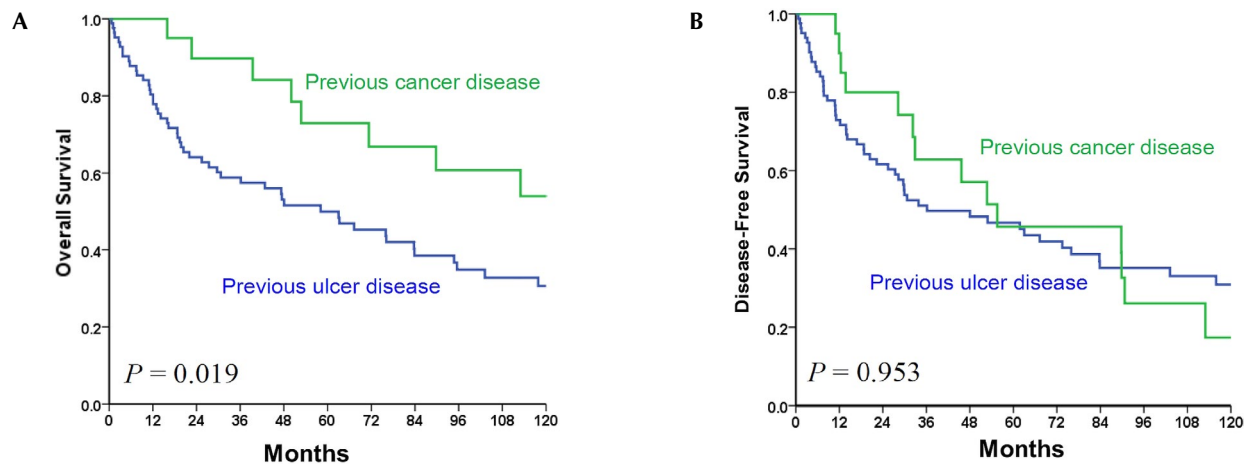
FIGURE 3 (A) Overall survival (months) for patients with gastric stump cancer after prior peptic ulcer disease or after prior gastric cancer (log-rank *p* = 0.019). (B) Disease-free survival (months) for patients with gastric stump cancer after prior peptic ulcer disease or after prior gastric cancer (log-rank *p* = 0.953).

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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