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Original Article

The Incidence and Risk Factors for Metachronous Gastric Cancer in the Remnant Stomach after Gastric Cancer Surgery

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Background/Aims: Less invasive surgical treatment is performed in East Asia to preserve postoperative digestive function and reduce complications such as postgastrectomy syndromes, but there is an issue of metachronous gastric cancer (GC) in the remaining stomach. This study aimed to analyze the incidence of metachronous GC and its risk factors in patients who had undergone partial gastrectomy.

Methods: A total of 3,045 GC patients who had undergone curative gastric partial resection at Seoul National University Bundang Hospital were enrolled and analyzed retrospectively for risk factors, including age, sex, smoking, alcohol, *Helicobacter pylori* status, family history of GC, histological type, and surgical method.

Results: Metachronous GC in the remaining stomach occurred in 35 of the 3,045 patients (1.1%): 23 in the distal gastrectomy group (18 with Billroth-I anastomosis, five with Billroth-II anastomosis), seven in the proximal gastrectomy (PG) group, and five in the pylorus-preserving gastrectomy (PPG) group. Univariate and multivariate Cox regression analyses showed that age ≥60 years (p=0.005) and surgical method used (PG or PPG, p<0.001) were related risk factors for metachronous GC, while male sex and intestinal type histology were potential risk factors.

Conclusions: Metachronous GC was shown to be related to older age and the surgical method used (PG or PPG). Regular and careful follow-up with endoscopy should be performed in the case of gastric partial resection, especially in patients with male sex and intestinal type histology as well as those aged ≥60 years undergoing the PG or PPG surgical method. **(Gut Liver 2022;16:366-374)**

Key Words: Stomach neoplasms; Epidemiology; Gastrectomy; Neoplasms, second primary

INTRODUCTION

Gastric cancer (GC) is common in East Asia, and South Korea's incidence of GC is still the highest in the world although the survival rate is improving significantly, as early diagnosis increases due to the national screening project for GC and the endoscopic and surgical treatment techniques for GC has improved.[1,2] The standard gastrectomy procedures for GC are distal gastrectomy (DG) and total gastrectomy, and less invasive surgical treatment has been performed in East Asia to preserve postoperative digestive function and reduce complications such as postgastrectomy syndromes.[3-7] Various procedures are being attempted, including proximal gastrectomy (PG), pylorus-preserving gastrectomy (PPG), and function-preserving gastrectomy.[8,9] As there is remaining stomach after operation, a possibility of metachronous GC exists. The incidence rate of metachronous GC may be higher than that of primary GC, since the gastric mucosa of patients with a history of GC is thought to have tumor microenvironment conditions such as genetic predisposition and damage caused by the gastric environment, relative to the gastric mucosa of people with-

out history of GC.[10,11] Therefore, careful follow-up of the remnant stomach after surgery is required. However, there have been few reports of the incidence or distribution of this type of GC after gastrectomy, none in Korea so far. We hypothesized that there are risk factors for the metachronous GC. From this background, the aim of this study was to analyze the incidence of this type of GC and its risk factors in patients who underwent gastrectomy.

MATERIALS AND METHODS

1. Patients

From May 2003 to January 2018, 3,707 patients' data were collected who were diagnosed with GC and surgically treated at Seoul National University Bundang Hospital (SNUBH). Among them, 3,045 patients who underwent curative gastric partial resection were enrolled. Those who underwent total gastrectomy, palliative debulking surgery, who were finally diagnosed with other cancer than gastric adenocarcinoma, or who were lost to follow-up were excluded (Fig. 1). Two thousand eight hundred one patients received DG, 146 patients received PG, and 98 patients received PPG or segmental gastric resection (Fig. 1). The medical records of these patients were collected using Clinical Data Warehouse of SNUBH and electronic medical record, including age, sex, smoking, alcohol, *Helicobacter pylori* (HP) status, presence of intestinal metaplasia, family history of GC, histological types, and surgical method.

2. Follow-up and HP eradication therapy

We defined metachronous GC as a newly diagnosed cancer that occurred in areas unrelated to surgery, at least 1 year after the surgery during the follow-up period to distinguish it from simultaneous GC (cancer found within 1 year of surgery) and recurrence (cancer associated with prior surgery, such as anastomosis or peritoneal metastasis), referring to previous studies.[12-14] Scheduled endoscopic follow-ups were conducted for 5 years, with 6 months interval for the first year and with 1 year interval for the next 4 years, and the diagnosis was made by histologic confirmation after operation. There was no difference in follow-up depending on the surgical methods used.

Atrophic gastritis and intestinal metaplasia were regarded as positive if they were identified in the endoscopic biopsy specimens of mucosa of the antrum or body and considered as negative if such findings did not exist on the specimens. In most patients, atrophic gastritis and intestinal metaplasia were confirmed through endoscopic biopsy samples performed just before surgery, and in patients without preoperative biopsy, biopsy samples performed at the first follow-up within 6 months of surgery were used.

HP-positive subjects were treated with initial eradication therapy, which consisted of triple therapy before 2012 and 10-day sequential therapy was frequently performed since 2012,[15] as our team found the rapid decrease of eradication rate of triple therapy with an increase of resistance of clarithromycin.[16] The triple therapy regimens consisted of a combination of a standard dose of esomeprazole 40 mg twice per day, amoxicillin 1 g twice per day, and clar-

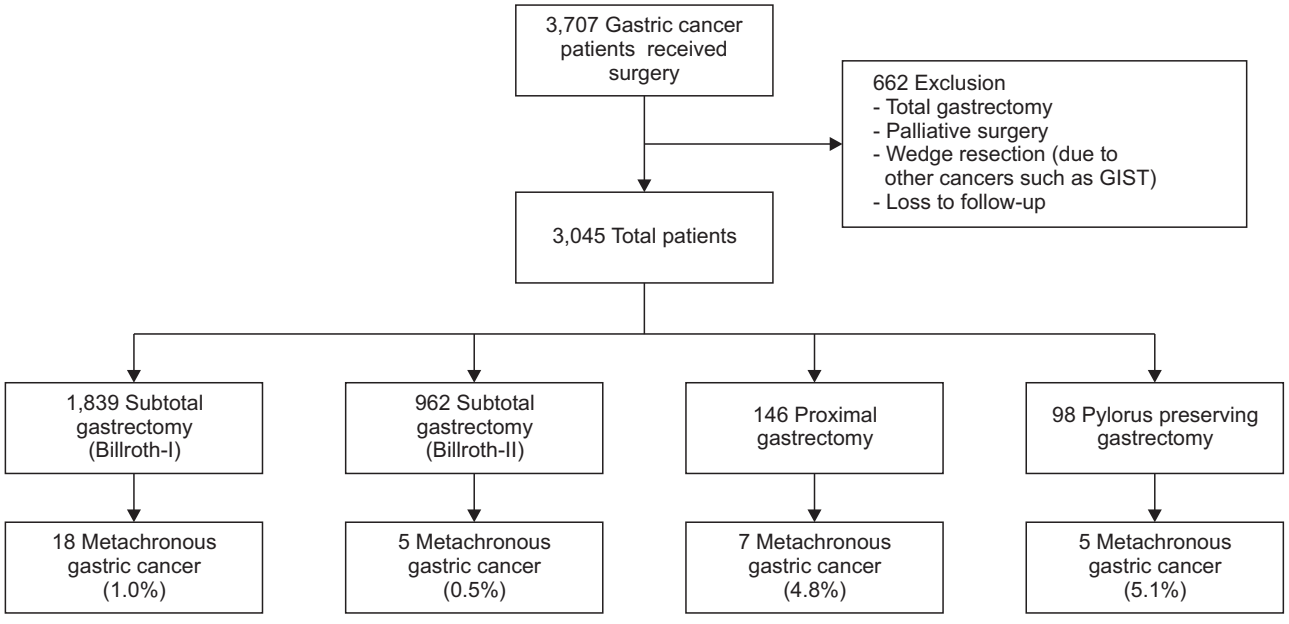

Fig. 1. Study flowchart.
GIST, gastrointestinal stromal tumor.

ithromycin 500 mg twice per day for 1 week. The 10-day sequential therapy included esomeprazole 40 mg, amoxicillin 1,000 mg twice per day for 5 days followed by esomeprazole 40 mg, clarithromycin 500 mg and metronidazole 500 mg twice per day for the next 5 days. The assessment of HP eradication was performed by a ^{13}C-urea breath test (UBiTkit; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) 4 weeks after the eradication therapy (if there was a possibility of false-positive then follow-up gastroscopic biopsy was performed again) or by histology (Giemsa stain) and rapid urease test when the follow-up gastroscopy was scheduled soon. The patients chose another eradication therapy if the first-line regimen failed: either a 14-day quadruple regimen containing bismuth (esomeprazole 40 mg twice per day, tripotassium dicitrate bismuthate (Denol; Green Cross Corp., Yongin, Korea) 300 mg four times per day, metronidazole 500 mg three times per day and tetracycline 500 mg four times per day) or a 14-day moxifloxacin-based triple therapy (moxifloxacin [Avelox; Bayer AG, Leverkusen, Germany] 400 mg daily, esomeprazole 40 mg twice per day, and amoxicillin 1 g twice per day).[17]

3. Consent and institutional review board

All patients provided written informed consent to participate in this study. The study was performed in accordance with the 53rd World Medical Association Declaration of Helsinki. The study was reviewed and approved by the Institutional Review Board (IRB) of SNUBH (IRB number: B-1902–523-107), and this study protocol has been registered at ClinicalTrials.gov (NCT 03978481).

4. Statistical analysis

Statistical analyses were performed using the Student t-test, the Pearson chi-square test, analysis of variance, Cox univariate and multivariate regression model via SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA) program.

Table 1. Baseline Characteristics

Variable	Patients with metachronous GC (n=35)	Patients without metachronous GC (n=3,010)	p-value
Sex			0.100
Female	7	998	
Male	28	2,012	
Age, mean±SD, yr	66.09±7.58	60.10±12.38	<0.001*
Family history of GC			0.918
No	29	2,514	
Yes	6	496	
Smoking status			0.253
No	16	1,668	
Yes	19	1,342	
Alcohol drinking			0.960
No	19	1,648	
Yes	16	1,362	
Gastric atrophy			0.026*
Absent	21	2,293	
Present	14	717	
Intestinal metaplasia			0.002*
Absent	13	1,879	
Present	22	1,131	
Histologic type (Lauren's classification)			0.008*
Intestinal	28	1,650	
Diffuse	5	1,190	
Mixed or undifferentiated	2	170	
Helicobacter pylori status			0.368
Eradicated	10	771	
Negative	20	1,408	
Positive (not treated)	5	831	
Surgical method for initial GC			<0.001*
Billroth-I	18	1,821	
Billroth-II	5	957	
Proximal gastrectomy	7	139	
Pylorus-preserving gastrectomy	5	93	

GC, gastric cancer.
*Statistically significant, p<0.05.

RESULTS

1. Incidence and clinicopathological characteristics of patients with metachronous GC

Of the 3,045 patients analyzed, metachronous GC occurred in 35 patients (1.1%). According to surgical method they were found to be 23 in the DG group (18 with Billroth-I anastomosis and five with Billroth-II anastomosis), seven in the PG group, and five in the PPG group (Fig. 1). Baseline characteristics of the patients are shown in Table 1. There were differences in the mean age, presence of intestinal metaplasia, histologic type and surgical methods used between patients with and without metachronous gastric neoplasm (MGN). The number of metachronous cancer patients according to the stage of primary cancer at the time of surgery was as follows: IA 25/1,773 (1.4%), IB 4/448 (0.9%), IIA 4/309 (1.3%), and IIB 2/175 (1.1%). Statistical significance was not observed (p=0.998 using the Cox regression analysis).

The time interval from initial cancer surgery to diagnosis of metachronous GC was median 50 months, maximum 156 months. The average time interval according to the surgical methods used was as follows: 63 months in Billroth-I group, 46 months in Billroth-II group, 55 months in PG group, and 48 months in PPG group. Statistical significance was not confirmed since the number of each group was too small.

2. Risk factors of metachronous GC

Multiple variables including sex, age, family history of GC, history of smoking and alcohol drinking, presence of gastric atrophy or intestinal metaplasia, histologic type of

Table 2. Risk Factors for Metachronous Gastric Cancer

Variable	Univariate analysis		Multivariate analysis	
	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Sex		0.048*		0.266
Female	Reference		Reference	
Male	2.30 (1.01–5.29)		1.62 (0.69–3.81)	
Age		0.002*		0.018*
<60 yr	Reference		Reference	
≥60 yr	3.74 (1.63–8.56)		2.78 (1.19–6.49)	
Family history of GC		0.975		
No	Reference			
Yes	0.99 (0.41–2.38)			
Smoking status		0.156		
No	Reference			
Yes	1.62 (0.83–3.15)			
Alcohol drinking		0.992		
No	Reference			
Yes	1.00 (0.51–1.94)			
Gastric atrophy		0.129		
Absent	Reference			
Present	1.69 (0.86–3.33)			
Intestinal metaplasia		0.011*		0.133
Absent	Reference		Reference	
Present	2.43 (1.23–4.84)		1.71 (0.85–3.46)	
Histologic type (Lauren's classification)		0.014*		0.189
Intestinal	Reference		Reference	
Diffuse	0.24 (0.09–0.63)		0.40 (0.15–1.08)	
Mixed or undifferentiated	0.66 (0.16–2.80)		0.77 (0.18–3.35)	
Helicobacter pylori		0.087		0.429
Eradicated	Reference		Reference	
Negative	2.18 (1.00–4.75)		1.69 (0.75–3.82)	
Positive (not treated)	1.02 (0.34–3.02)		1.19 (0.39–3.60)	
Surgical method for initial GC		<0.001*		<0.001*
Billroth-I	Reference		Reference	
Billroth-II	0.65 (0.29–2.16)		0.84 (0.31–2.29)	
Proximal gastrectomy	7.60 (3.10–18.61)		6.71 (2.66–16.94)	
Pylorus-preserving gastrectomy	10.27 (3.66–28.81)		8.93 (3.12–25.54)	

aHR, adjusted hazard ratio; CI, confidence interval; GC, gastric cancer.
*Statistically significant, p<0.05.

initial GC, HP status, and surgical methods used were analyzed using the Cox regression analyses, and the results are shown in Table 2. In the Cox univariate analysis, male sex (adjusted hazard ratio [aHR], 2.30; p=0.048), age ≥60 years (aHR, 3.74; p<0.001), presence of intestinal metaplasia (aHR, 2.43; p=0.011), intestinal type histology (p=0.014), and surgical methods used (aHR of PG, 7.60; aHR of PPG, 10.27; p<0.001) were potential risk factors, and the Cox multivariate analysis revealed only age ≥60 years (aHR, 2.78; p=0.018) and surgical methods used (aHR of PG, 6.71; aHR of PPG, 8.93; p<0.001) were independent risk factors for metachronous GC (Table 2). In terms of the correlation between metachronous GC and HP, 10 out of 35 patients received postoperative HP eradication treatment after initial surgery, 20 patients were negative for HP, and five patients were HP positive at the time of metachronous cancer occurrence (they did not receive eradication treatment). Although the incidence of metachronous GC in HP negative patients was somewhat high in the Cox univariate analysis (aHR, 2.18; p=0.087), multivariate analysis did not confirm a statistical significance.

We did additional analyses targeting patients who underwent DG, since DG procedure is the most common procedure, and the characteristics of the cancer can vary depending on the location of the tumor. The results are demonstrated in Supplementary Table 1. In the Cox univariate analysis, age ≥60 years (aHR, 3.30; p=0.019) was a potential risk factor. However, statistical significance was not seen in the Cox multivariate analysis since the number of metachronous GC cases had decreased.

3. Clinicopathological characteristics of patients with metachronous GC

Clinicopathological characteristics of metachronous GC are demonstrated in Table 3. Thirty cases of metachronous GC were early GCs and five cases were advanced GCs. The location of initial GC was as follows: cardia (three cases), fundus (one case), body (16 cases), and antrum (15 cases). Most of them (33/35 cases, 94%) were completely curable, as they were treated with endoscopic resection (10 cases) and remnant total gastrectomy (23 cases). Among them, two patients underwent additional surgery after incomplete endoscopic resection for metachronous lesion. Only two patients were treated with systemic chemotherapy, who were unable to receive curative resection because of disease progression or other comorbidities (Table 3).

The histologic types of metachronous GCs were as follows: intestinal type (23 cases), diffuse type (six cases), and mixed type (one case). In five patients, histologic types could not be identified due to non-operational or omission of biopsy results. Statistical significance was not observed between the tumor location and the histologic type of metachronous cancer (p=0.269 using the bivariate correlation analysis).

Table 3. Clinicopathological Characteristics of Patients with Metachronous Gastric Cancer

Patients with metachronous GC (n=35)	No. (%)
Type of metachronous GC	
Early GC	30 (85.7)
Advanced GC	5 (14.3)
Surgical method for initial GC	
Billroth-I	18 (51.4)
Billroth-II	5 (14.3)
Proximal gastrectomy	7 (20.0)
Pylorus-preserving or segmental gastrectomy	5 (14.3)
Treatment modality for metachronous GC	
Endoscopic resection (EMR or ESD)	10 (28.6)
Surgical resection after endoscopic resection	2 (5.7)
Surgical resection (remnant total gastrectomy)	21 (60.0)
Chemotherapy	2 (5.7)
Helicobacter pylori status at time of metachronous GC diagnosis	
Eradicated (after initial GC surgery)	10 (28.6)
Negative (persistently negative)	20 (57.1)
Positive	5 (14.3)
Location of initial GC	
Cardia	3 (8.6)
Fundus	1 (2.9)
Body	16 (45.7)
Antrum	15 (42.9)

GC, gastric cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

DISCUSSION

In this study, the overall incidence of metachronous GC was 1.1%, and the incidence was much higher in PG and PPG groups. The Cox univariate and multivariate analyses revealed that age ≥60 years and surgical methods used (PG or PPG) were independent risk factors, while male sex and intestinal type histology would be potential risk factors. This is the first report regarding metachronous GC after surgery for GC in Korea, so far.

It is ideal to minimize the resected range as possible, and gastric partial resection is a useful treatment option because it has the advantage of preserving reservoir, digestive function, body weight and reducing postoperative complications such as postgastrectomy syndrome, gallstones and anemias, with similar cancer recurrence and postoperative mortality, although there is risk of metachronous GC in the remaining stomach.[9,18,19] The incidence and related risk factors of metachronous GC, and time from initial gastrectomy to metachronous GC diagnosis have been unclear yet.[10,11,20,21]

Reviewing the results of previous studies about metachronous GC after partial gastric resection, the incidence of metachronous GC varies wide, as 1% to 2% after DG,[22-27] and 6% to 10% after PG or PPG.[13,28,29] In the recently published nationwide study in Japan, the precise incidence of metachronous GC was estimated to be 2.35% after DG, 3.01% after PPG, 6.28% after PG and 8.21% after function-preserving gastrectomy, respectively.[30] In our data, the incidence was 0.8% after DG, 4.7% after PG and 4.1% after PPG, higher in patients who received PG or PPG with statistical significance. The lower prevalence of metachronous GC in this study is believed to be due to that only GC occurred in areas unrelated to anastomosis site after at least 1 year of surgery, since there is a possibility of simultaneous cancer which have been missed at the time of diagnosis in the case of GC found within a year after surgical resection of initial cancer.[14,31-33] Also, regular endoscopic follow-up with radical resection of precancerous lesions such as gastric adenoma was performed in our hospital.[33] In this report, MGN developed in 7.4% in the 257 patients with gastric neoplasm (113 low-grade dysplasias, 25 high-grade dysplasias, and 119 early GCs) during a mean follow-up of 52 months.[34] Multivariate analysis showed that moderate/severe corpus intestinal metaplasia and family history of GC were independent risk factors for MGN development; the hazard ratios were 4.12 (95% confidence interval, 1.23 to 13.87; p=0.022) and 3.52 (95% confidence interval, 1.09 to 11.40; p=0.036), respectively. The methylation level of *MOS* in the CpG sites which as correlated with severity of intestinal metaplasia[35,36] was significantly elevated in patients with MGN compared age- and sex-matched patients without MGN (p=0.020). In another similar study regarding risk of MGN occurrence after endoscopic submucosal dissection for gastric dysplasia showed that MGNs developed in 21 patients (10.6%) in the low-grade dysplasia group and in six patients (13.0%) in the high-grade dysplasia group.[37] In the present study the overall incidence of metachronous GC was 1.1%, which is lower rate of MGN after endoscopic treatment. It could be a meaningful result that a higher incidence rate of metachronous GC was observed in patients with PG or PPG compared to patients with DG.

Previously known risk factors for metachronous GC were male sex,[21,28,29] PG,[13,28] older age, invasion of submucosal layer,[13] intestinal type histology,[21] and macroscopic type (O-IIa).[29] In this study, male sex, older age, presence of intestinal metaplasia, intestinal type histology and surgical methods (PG or PPG) were potential risk factors. In addition, multivariate analyses revealed that older age and surgical methods (PG or PPG) as risk factors for metachronous GC, respectively. Previous studies have suggested possibilities for high incidence of MGN after PG or PPG. There might be several reasons for this result. First, the area of the gastric mucosa left after PG is much wider, as one-fifth to one-third of the proximal stomach is preserved with the DG or the PPG,[38] while one-half to two-thirds of the distal stomach is preserved with the PG.[39] Second, the antrum has a higher rate of GC than the body, with the possibility that the lower third of the stomach has more foci of multicentric carcinogenesis than the upper third of the stomach.[13,40] Third, the reduction of bile reflux and the increased effects of HP infection after PG or PPG could be the reason.[28] It is well known that eradication of HP is needed to prevent metachronous GC after endoscopic resection of early GC,[41] but it is not yet clear about HP eradication and metachronous GC incidence after gastrectomy, with no statistically significant connection has been reported so far. Further research is needed considering that HP contributes to stomach cancer. Another explanation could be hypergastrinemia which plays a role in the occurrence of metachronous GC. G cells that secret gastrin are distributed in the antrum.[28,42-44] In addition to these, another reason might be that thorough examination of remnant stomach and resection of lesion are more difficult in patients after PG, especially in cases with long efferent loop. In several studies, male sex has been reported as a risk factor for metachronous GC, and although no precise mechanism is known, intestinal type histology is believed to be associated with this.[21] In our data, although not statistically significant, male sex and intestinal type histology have been shown to be potential risk factors for metachronous GC.

This study has several limitations. First, this was a retrospective study and the number of patients with metachronous GC were small as it was conducted by a single institution, although over 3,000 patients from more than 15 years of study period were enrolled. Multicenter trial with a larger number of metachronous GC patients including the influence of other risk factors such as HP would be needed. Second, study with longer period is needed, since metachronous GC can still occur 10 years after surgery.[13,21] However, there were cases that occurred more than 12 years after initial surgery in our data. Third, not only the occurrence of metachronous cancer but also the occurrence of dysplasia, a precursor to cancer, is clinically important. Unfortunately, we could not analyze data for gastric adenoma cases in this study since it was very difficult to find out the metachronous adenoma cases from Clinical Data Warehouse mainly because it was hidden under the diagnosis of GC category, and the total number of patients are approximately 3,700. Instead, we reviewed the previous reports. There were no studies of the incidence of MGNs including adenoma after partial gastrectomy so far, and most of the literature deals only with the cancer. However, several reports analyzed MGN including adenoma after endoscopic therapy for the GC. Previously, we report that the incidence of metachronous neoplasm after endoscopic resection (endoscopic mucosal resection or endoscopic submucosal dissection) was 7.4% (19/259; 12 adenomas and seven adenocarcinomas)[34] and 16.1% (13 adenomas and seven adenocarcinomas), in a subsequent study being performed. Referring to other studies reported in Korea, the number of metachronous adenomas and cancers after DG was 18 and 12 (however, in this study, the incidence of metachronous neoplasms could not be identified since only cases treated with endoscopic submucosal dissection were collected).[45] And Kim *et al.*[37] reported that the incidence of metachronous neoplasms after endoscopic treatment for gastric dysplasia was 11.0%, and the number of metachronous adenomas and cancers was 24 (18 low-grade adenomas and six high-grade adenomas) and three, respectively. Although the number of MGNs in patients received surgery might be smaller due to the decreased area of the remnant stomach after surgery, the ratio of adenoma and cancer could be similar. Later, it will need to be analyzed through a follow-up study that includes both adenoma and cancer. Finally, HP was diagnosed and identified through repeated endoscopic biopsy in most subjects. However, due to practical difficulties such as patients who were not possible to undergo endoscopy again, histologic tests such as Giemsa stain for HP were not performed.

In conclusion, metachronous GC was diagnosed in 1.1% of patients who underwent partial gastric resection and was related to older age and surgical methods used (PG or PPG). Male sex and intestinal type histology were potential risk factors for metachronous GC. Regular and careful follow-up with endoscopy should be premised in the case of gastric partial resection, especially in patients accompanied by these risk factors.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: N.K., H.H.K. Data curation: Y.C., H.H.K. Formal analysis: Y.C., N.K. Funding acquisition: N.K. Methodology: Y.S.P., S.H.A., Y.S.S., D.J.P., H.H.K. Project administration: N.K., H.H.K. Visualization: H.Y., C.M.S., Y.S.P., D.H.L. Writing - original draft: Y.C. Writing - review & editing: N.K., H.Y., C.M.S., Y.S.P., D.H.L. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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