

Clinical Outcomes of Metachronous Gastric Cancer after Endoscopic Resection for Early Gastric Cancer

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See editorial on page 145.

Background/Aims: Patients treated with endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) are at risk of developing metachronous gastric cancer (MGC). The aim of this study was to evaluate the clinical outcomes of MGC after ESD for EGC between the re-ESD and surgery groups. **Methods:** In total, data from 1,510 patients who underwent ESD for EGC from January 2005 to May 2014 were retrospectively reviewed, and data from 112 patients with MGC were analyzed according to the type of treatment, namely, re-ESD and surgery. The clinicopathological factors affecting the subsequent treatment and outcomes of MGC were evaluated. **Results:** The median duration to the development of MGC was 47 months. In multivariate analysis, lower body mass index (BMI) ($p=0.037$) and multiplicity ($p=0.014$) of index cases were significantly associated with subsequent surgery for MGC. In cases of MGC, a diffuse or mixed-type Lauren classification ($p=0.009$), the depth of tumor mucosal invasion ($p=0.001$), and an upper stomach location ($p=0.049$) were associated with surgery. Overall survival was significantly shorter in the surgery group than in the re-ESD group after treatment for MGC (log-rank test, $p=0.01$). **Conclusions:** Lower BMI and multiplicity of index cancers were significantly associated with the surgical resection of MGC. Close follow-up is needed to minimize additional treatment for cases at high risk of advanced MGC after ESD for EGC. (*Gut Liver* 2020;14:190-198)

Key Words: Early gastric cancer; Endoscopic submucosal dissection; Metachronous gastric cancer; Surgery; Survival rate

INTRODUCTION

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death in the world.¹ Endoscopic submucosal dissection (ESD) has been widely used for early gastric cancer (EGC) in Korea and Japan since the late 1990s.² However, as endoscopic resection spares the gastric mucosa in patients with EGC, it has a potential risk of metachronous gastric cancer (MGC).³

MGC is usually considered as a developed gastric cancer located distant from the initial EGC after 1 year following index ESD. Previous studies have reported the incidence of MGC following endoscopic resection for EGC ranging from 2.7% to 15.6%.⁴ Because the incidence of MGC increases as time passes, continuing surveillance is necessary for the detection of MGC even after curative ESD.⁵

Treatment modality for MGC, surgery or re-ESD, is generally determined by the same indications of index EGC. Previous study has reported that 90.3% of patients with MGC received re-ESD and 5.9% received surgery.⁵ However, there has been little data of characteristics of index cancer associated with occurrence of MGC in terms of risk of lymph node (LN) metastasis, and clinical outcomes between re-ESD and surgery group for MGC.

The aim of this study was to evaluate the risk factors and clinical outcomes of MGC between re-ESD and surgery group.

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MATERIALS AND METHODS

1. Patients

Patients who had undergone ESD for gastric neoplasms and been diagnosed as EGC in final pathology from January 2005 through May 2014 at Seoul National University Hospital were retrospectively reviewed. Indications for ESD were as follows: biopsy-proven adenoma, and differentiated adenocarcinoma with gross tumor size ≤ 2 cm and no evidence of submucosal invasion or metastasis to LNs or other distant organ. Curative resection was defined as an *en bloc* resection with tumor-negative margin, without evidence of lympho-vascular invasion, and within the expanded criteria. Expanded criteria were defined as follows: (1) differentiated mucosal cancer without ulcer regardless of size; (2) differentiated mucosal cancer ≤ 3 cm with ulcer; (3) undifferentiated mucosal cancer ≤ 2 cm; or (4) differentiated submucosal (SM)1 (tumor invasion < 500 μm from the muscularis mucosa) cancer ≤ 3 cm.⁶ In the cases of non-curative resection, additional surgical resection was recommended in principle, which might be waived in exceptional cases with underlying severe co-morbidity, old age (> 80 years), or patients' preference. MGC was defined as a newly developed cancer at other site from index cancer in stomach beyond 1 year after index ESD, and included both metachronous EGC and advanced gastric cancer (AGC). ESD indications for MGC were applied of the same method as index EGC. Metachronous EGC with non-curative resection and metachronous AGC was treated by sur-

gery.

Patients were excluded if they had gastrectomy within 12 months after index ESD or follow-up period less than 12 months. The patients with MGC were divided into two groups; re-ESD and surgery group. Demographic data were achieved from medical records, including age, sex, body mass index (BMI), and pathological data of index cancer and MGC; atrophy, intestinal metaplasia, *Helicobacter pylori* status, tumor findings (gross type, multiplicity, Lauren type, differentiation, depth of invasion, vertical location, size, presence of ulcer, lympho-vascular invasion, and resection margin). The Institutional Review Board of the Seoul National University Hospital approved this study (IRB number: H1612-103-815). Patient consent was waived, given the retrospective nature of this study.

2. Methods of ESD, pathologic evaluation and endoscopic follow-up

All ESD procedures were performed using a standard single-channel endoscope (Olympus H260; Olympus Optical, Tokyo, Japan), as previously described.⁷ Briefly, after marking at 5-mm outside of the lesion, circumferential incision was done outside the marking and dissection was performed beneath submucosal layer using an insulation-tipped knife (Helmet Snare; Kachu Technology Co., Seoul, South Korea).

The specimens were evaluated with sections of 2- and 4-mm thickness after ESD and surgical resection, respectively, stained with hematoxylin and eosin. Histologic evaluation was per-

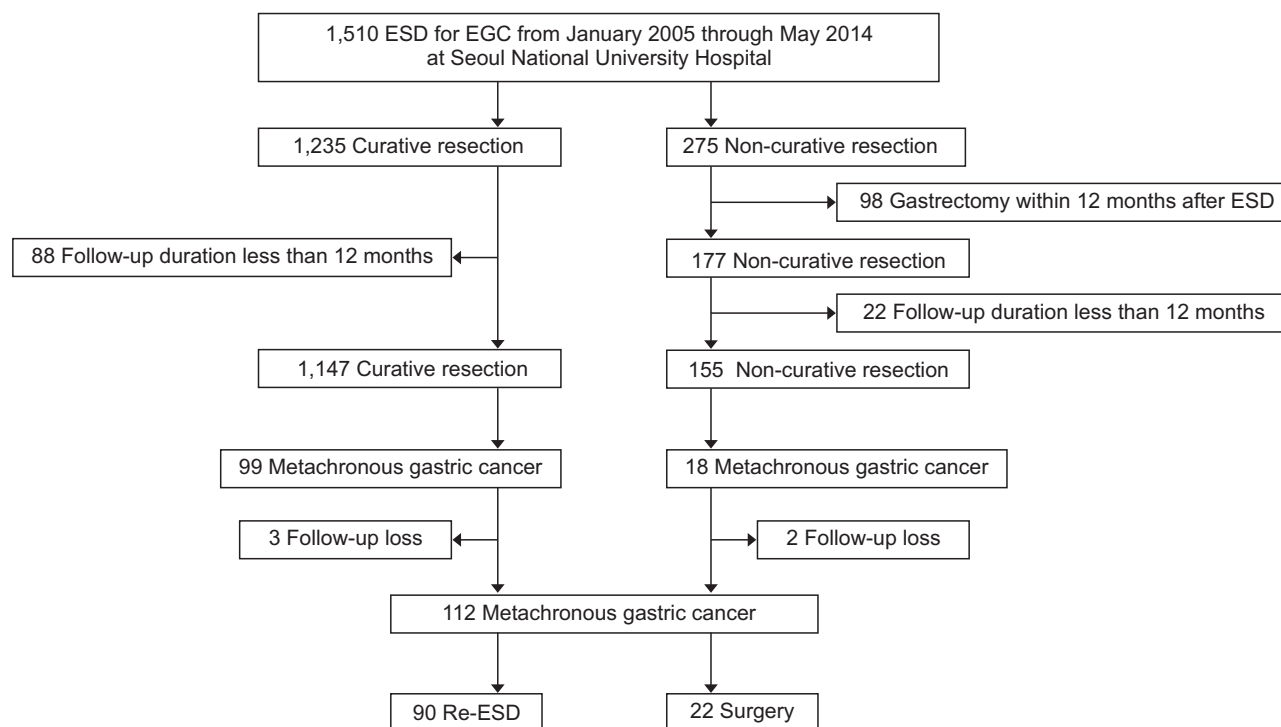


Fig. 1. Study flowchart showing patient enrollment. ESD, endoscopic submucosal dissection; EGC, early gastric cancer.

formed from the antrum and body in terms of *H. pylori* status, mucosal atrophy/intestinal metaplasia both at the diagnosis of index cancer and MGC. Histological grades of mucosal atrophy and intestinal metaplasia were reported using the Updated Sydney System. The scores were defined as normal (0), mild (1), moderate (2), and marked (3), and moderate and marked grade were defined as positive. Rapid urease test (CLOtest®; Delta West Ltd., Bentley, Australia) was also conducted at antrum, and *H. pylori* status was judged as positive if histologic and/or rapid urease test was positive.

Follow-up endoscopies after ESD were scheduled at 3, 6, 12 months, and annually thereafter. On the other hand, follow-up endoscopies after surgery were conducted annually. The follow-up period was calculated as the interval between index ESD/treatment for MGC and the last endoscopic follow-up.

Overall survival (OS) was defined as the period from the date of ESD/surgery for MGC until all death.

3. Statistical analysis

Re-ESD and surgery group were compared for demographic and clinicopathological data using the Pearson chi-square test, Fisher exact test, Mann-Whitney U test, Student t-test, and logistic regression model. Multivariate analysis included statistically significant ($p < 0.05$) and clinically important covariates in the univariate analysis using the logistic regression model. The cumulative incidences of metachronous carcinoma were calculated using the Kaplan-Meier method with a log-rank test. All statistics were analyzed using the Statistical Package for the Social Sciences, version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Study population and cumulative incidence of MGC occurrence

A total of 1,510 patients who had undergone ESD for EGC from January 2005 through May 2014 at Seoul National University Hospital were included in this retrospective cohort study, of whom 208 patients were excluded; 98 patients with gastrectomy within 12 months after ESD, and 110 patients lost to follow-up within 12 months after ESD.

In 1,302 eligible patients, curative resection was achieved in 1,147, and non-curative resection in 155. The mean follow-up duration was 66 ± 30 months (range, 12 to 156 months). During follow-up period, MGC had developed in 117 patients (9%), of whom 90 patients underwent re-ESD, 22 surgery, and five lost to further treatment. In the surgery group, three patients had received additional surgical resection after re-ESD by the final result of pathological mapping beyond expanded indication (Fig. 1).

In the Kaplan-Meier analysis, the median duration to MGC development was 47 months (interquartile range, 30 to 67 months), which gradually increased as time passed (Fig. 2A). There was no significant difference in the cumulative incidence of MGC between curative resection and non-curative resection group ($p = 0.221$ in log-rank test) (Fig. 2B)

2. Clinicopathological characteristics of index cancer affecting treatment for MGC

Males were predominant in both groups; re-ESD (74/90, 82.2%) and surgery (17/22, 77.3%) (Table 1). Patients in re-ESD group had significantly higher BMI ($p = 0.025$) and moderate to severe intestinal metaplasia ($p = 0.029$) than surgery group. However, there were no significant differences in other index clinicopathological characteristics between surgery and re-ESD

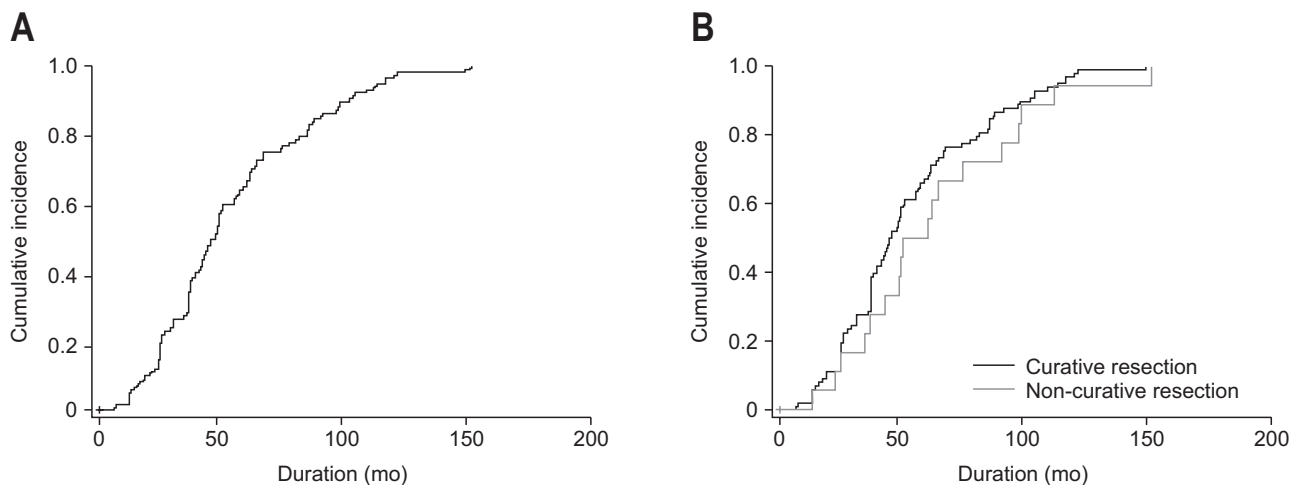


Fig. 2. Cumulative incidence of metachronous gastric cancer (MGC) after endoscopic submucosal dissection (ESD). (A) Cumulative incidence of MGC after ESD and (B) cumulative incidence of MGC after ESD (curative resection versus noncurative resection).

Table 1. Baseline and Index Tumor Characteristics of the Re-ESD and Surgery Groups

Baseline and index tumor characteristics	Overall (n=112)	Re-ESD (n=90)	Surgery (n=22)	p-value
Clinical characteristics				
Age, yr	64.5±9.5	64.7±9.6	63.6±8.9	0.596
Sex male	91 (81.3)	74 (82.2)	17 (77.3)	0.594
BMI, kg/m ²	24.5±2.7	24.7±2.7	23.3±2.4	0.025
Pathologic characteristics at index cases				
Index <i>H. pylori</i> infection				0.242
Positive	58 (51.8)	49 (54.4)	9 (40.9)	
Negative	44 (39.3)	32 (35.6)	12 (54.5)	
Atrophy*				0.891
Moderate to marked	43 (38.4)	35 (38.9)	8 (36.4)	
Absent to mild	46 (41.1)	36 (40)	10 (45.5)	
Intestinal metaplasia				0.029
Moderate to marked	79 (70.5)	67 (74.4)	12 (54.5)	
Absent to mild	23 (20.5)	14 (15.6)	9 (40.9)	
Gross type				0.754
Elevated	44 (39.3)	36 (40)	8 (36.4)	
Non-elevated	68 (60.7)	54 (60)	14 (63.6)	
Multiple cancer				0.09
One	102 (91.1)	84 (93.3)	18 (81.8)	
Multiple (>1)	10 (8.9)	6 (6.7)	4 (18.2)	
Lauren type				0.054
Intestinal	106 (94.6)	87 (96.7)	19 (86.4)	
Diffuse or mixed	6 (5.4)	3 (3.3)	3 (13.6)	
Differentiation type				0.054
Differentiated	106 (94.6)	87 (96.7)	19 (86.4)	
Undifferentiated	6 (5.4)	3 (3.3)	3 (13.6)	
Depth				0.147
T1m	104 (92.8)	83 (92.2)	22 (100)	
T1sm	8 (7.2)	7 (7.7)	0	
Tumor location				0.424
Upper	4 (3.6)	4 (4.4)	0	
Middle	27 (24.1)	23 (25.6)	4 (18.2)	
Lower	81 (72.3)	63 (70)	18 (81.8)	
Tumor size, mm	1.9±1.2	18.5±10.6	19.5±11.2	0.538
Ulcer*				0.527
Yes	3 (2.7)	3 (3.3)	0	
No	107 (95.5)	85 (94.4)	22 (100)	
Venous invasion				-
Yes	0	0	0	
No	112 (100)	90 (80.4)	22 (19.6)	
Lymphatic invasion				0.48
Yes	2 (1.8)	2 (2.2)	0	
No	110 (98.2)	88 (97.8)	22 (20)	

Table 1. Continued

Baseline and index tumor characteristics	Overall (n=112)	Re-ESD (n=90)	Surgery (n=22)	p-value
Vertical resection margin				0.276
Positive	2 (1.8)	1 (1.1)	1 (4.5)	
Negative	110 (98.2)	89 (98.9)	21 (95.5)	
Curative resection				0.923
Yes	96 (85.7)	77 (85.6)	19 (86.4)	
No	16 (14.3)	13 (14.4)	3 (13.6)	
Duration from index ESD to diagnosis of metachronous cancer, mo	53.8±31.3	53.0±30.6	56.9±34.4	0.698

Data are presented as mean±SD or number (%).

ESD, endoscopic submucosal dissection; BMI, body mass index; *H. pylori*, *Helicobacter pylori*; m, mucosal cancer; sm, submucosal cancer.

*Exception where pathologic evaluation is inapplicable or medical record is absent.

Table 2. Multivariate Analysis of the Baseline and Index Tumor Characteristics in the Re-ESD and Surgery Groups

Baseline and index tumor characteristics	p-value	Exp (B)	95% CI for Exp (B)
BMI	0.037	0.744	(0.563–0.983)
Male sex	0.552		
Initial multiple cancer (yes)	0.014	29.131	(1.982–428.465)
Atrophy, index case (moderate to marked)	0.133		
Intestinal metaplasia, index case (moderate to marked)	0.226		
Index <i>H. pylori</i> infection (positive)	0.971		
Differentiation type (undifferentiated)	0.751		

ESD, endoscopic submucosal dissection; CI, confidence interval; BMI, body mass index; *H. pylori*, *Helicobacter pylori*.

groups for MGC. The median period to MGC occurrence after ESD was not associated with the type of treatment for MGC ($p=0.698$).

In multivariate analysis, lower BMI and multiplicity of index cases were significantly associated with surgery than re-ESD group (odds ratio [OR], 0.744; 95% confidence interval [CI], 0.563 to 0.983; $p=0.037$ and OR, 29.131; 95% CI, 1.982 to 428.465; $p=0.014$, respectively) (Table 2).

3. Treatment outcomes and prognosis of MGC between re-ESD versus surgery group

To compare the treatment outcomes of re-ESD with surgery group, we analyzed pathologic features of MGC of both groups. In surgery group, tumors invaded to proper muscle and over in four cases (18.1%). Tumor invasion to lymphatics was found in 13.6% of surgery and 4.4% of re-ESD group. In surgery group, tumors had LN metastasis in 22.7%. In univariate analysis, persistent *H. pylori* infection, intestinal type, differentiated histology, mucosal cancer, middle or lower location of stomach, and smaller tumor size were more common in re-ESD than surgery group (Table 3). In multivariate analysis, non-intestinal type, tumor invasion over mucosa, and upper location of stomach were more common in surgery than re-ESD group (Table 4). Persistent *H. pylori* infection was not associated with re-ESD or surgery group.

A total of seven patients of 112 patients (6.3%) died during a mean follow-up period of 66 ± 30 months. Mortality rate was higher in surgery (22.7%) than re-ESD group (2.2%), and OS was significantly higher in re-ESD than surgery group ($p=0.01$, log-rank test) (Fig. 3).

DISCUSSION

ESD has been regarded as the standard treatment for EGC in proper indication, and has a strong merit in terms of preservation of organ and maintenance of quality of life. Nevertheless, concerns about MGC still remain because the remnant gastric mucosa also has the risk of new tumor development even after endoscopic resection for EGC.⁴ The incidence of MGC after endoscopic resection has been reported to be 5.1% to 14%.^{8,9} In this study, MGC occurred in 9% during the median follow up of 66 months, which was similar to previous studies. Cumulative incidence of MGC had increased over time from 9.5% in 5 years to 22.7% in 10 years.⁵ The present study showed that the median time interval to MGC was 47 months, and the incidence of MGC had gradually increased up to 10 years, which suggests that endoscopic surveillance may be important for more than 10 years after endoscopic resection of EGC.

This retrospective study has strength in that it compared the index characteristics of two groups; re-ESD and surgery groups

Table 3. Treatment Outcomes of Re-ESD versus Surgery for MGC: Univariate analysis for the Pathological Features of Metachronous Cancer

Pathologic characteristics	Overall (n=112)	Re-ESD (n=90)	Surgery (n=22)	p-value
Persistent <i>H. pylori</i> infection				0.047
Negative or eradicated	50 (44.6)	38 (42.2)	12 (54.5)	
Persistent	40 (35.7)	37 (41.1)	3 (13.6)	
Unknown	22 (19.6)	15 (16.7)	7 (31.8)	
Atrophy				0.774
Moderate to severe	25 (22.5)	22 (24.4)	3 (13.6)	
Absent to mild	40 (36)	37 (41.2)	4 (18.1)	
Intestinal metaplasia				0.594
Moderate to severe	57 (51.3)	51 (56.7)	6 (27.3)	
Absent to mild	20 (17.9)	17 (18.9)	3 (13.6)	
Gross type				0.976
Elevated	10 (8.9)	8 (8.9)	2 (9.1)	
Non-elevated	102 (91.1)	82 (91.1)	20 (90.9)	
Multiple cancer				0.394
One	102 (91.1)	83 (92.2)	19 (86.4)	
Multiple (>1)	10 (8.9)	7 (7.8)	3 (13.6)	
Lauren type*				<0.001
Intestinal	81 (85.4)	72 (87.8)	10 (50)	
Diffuse or mixed	14 (14.6)	4 (28.6)	10 (50)	
Differentiation type				<0.001
Differentiated	96 (85.7)	85 (94.4)	11 (50)	
Undifferentiated	16 (14.3)	5 (5.6)	11 (50)	
Depth				0.001
T1m	88 (78.6)	77 (85.6)	14 (63.7)	
≥T1sm	24 (21.4)	13 (14.4)	8 (36.3)	
Tumor location				0.038
Upper	8 (7.1)	4 (4.4)	4 (18.2)	
Middle or lower	104 (92.9)	86 (95.6)	18 (81.8)	
Tumor size, mm	19.7±1.3	18±1	26.8±2	0.012
Ulcer [†]				<0.05
Yes	1 (0.9)	1 (1.1)	0	
No	92 (82.1)	89 (98.9)	10 (45.5)	
Venous invasion				0.999
Yes	1 (0.9)	0	1 (4.5)	
No	111 (99.1)	90 (100)	21 (95.5)	
Lymphatic invasion				0.129
Yes	7 (6.3)	4 (4.4)	3 (13.6)	
No	105 (5.4)	86 (95.6)	19 (86.4)	
Lymph node metastasis				-
Positive	-	-	5 (22.7)	
Negative	-	-	17 (77.3)	
Vertical resection margin				0.999
Positive	5 (4.5)	5 (5.6)	0	
Negative	104 (92.9)	84 (93.3)	20 (90.6)	
Unknown	3 (2.7)	1 (5.6)	2 (9.1)	

Table 3. Continued

Pathological characteristics	Overall (n=112)	Re-ESD (n=90)	Surgery (n=22)	p-value
Lateral resection margin				0.37
Positive	11 (9.8)	10 (11.1)	1 (4.5)	
Negative	101 (90.2)	80 (88.9)	21 (95.5)	

Data are presented as number (%) or mean±SD.

ESD, endoscopic submucosal dissection; MGC, metachronous gastric cancer; *H. pylori*, *Helicobacter pylori*.

*Exception where pathological reports are unknown or indeterminate; [†]Exception where pathologic evaluation is inapplicable or medical record is absent.

Table 4. Treatment Outcomes of Re-ESD versus Surgery for MGC: Multivariate Analysis for the Pathological Features of Metachronous Cancer

Pathological characteristics	p-value	Exp (B)	95% CI for Exp (B)
Persistent <i>H. pylori</i> infection	0.055	0.163	(0.026–1.038)
Lauren type (non-intestinal type)	0.009	11.176	(1.842–67.792)
Differentiation (undifferentiated)	-		
Depth of invasion (≥T1sm)	0.001	19.864	(3.329–118.506)
Tumor location (middle or lower part of stomach)	0.049	0.088	(0.008–0.991)
Tumor size	0.206		

ESD, endoscopic submucosal dissection; MGC, metachronous gastric cancer; CI, confidence interval; *H. pylori*, *Helicobacter pylori*; sm, submucosal cancer.

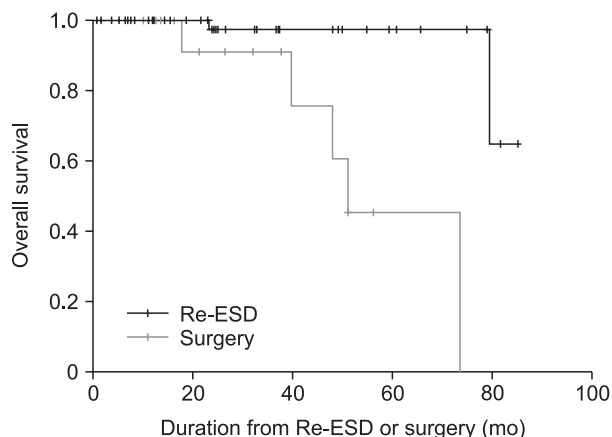


Fig. 3. Overall survival after re-ESD or surgery for metachronous gastric cancer: re-ESD versus surgery groups. ESD, endoscopic submucosal dissection.

for MGC. Clinicopathological characteristics of index tumor may influence on the development and treatment strategy of MGC. As the treatment of MGC was decided by the endoscopic and histologic characteristics itself, MGC with high risk of LN metastasis was preferentially allocated into surgery group. Therefore, it is important to identify the factors of index tumor that influenced the characteristics of MGC and the subsequent treatment. In addition, these relevant characteristics of index tumor might reflect the development of MGC in terms of the risk of LN metastasis.

Endoscopic resection has been applied to multiple EGCs meeting indications for endoscopic resection.¹⁰ Multiple gastric

cancers tend to be more susceptible to the development of MGC than solitary gastric cancers.⁵ Previous studies have reported that microsatellite instability was related with tumor multiplicity and might be an indicator for the occurrence of metachronous cancer.¹¹ However, there has been a debate whether microsatellite instability was associated with tumor aggressiveness and prognosis.^{12,13} In a previous study, multiple EGCs had similar incidence of LN metastasis as solitary cancer.¹⁰ In this study, index multiple cancer was significantly associated with advanced histology of MGC, eventually surgery group (OR, 29.131; 95% CI, 1.982 to 428.465; $p=0.014$). Meticulous follow-up may be essential to screen MGC in early stage in cases with initial multiple cancer.

It has been known that obesity is associated with gastric cancer, especially cardia cancer.¹⁴ However, confounding variables such as *H. pylori* infection were not corrected in the study. In a recent study, obesity increased the risk of well or moderately differentiated EGC regardless of *H. pylori* infection.¹⁵ In another study, obesity was significantly associated with the risk of non-cardia gastric cancer.^{15,16} In this study, BMI was significantly higher in re-ESD than surgery group (OR, 0.744; 95% CI, 0.563 to 0.983; $p=0.037$), which showed similar result with previous studies in that higher BMI was significantly associated with less aggressive histology of MGC.

H. pylori infection has been known to be a risk factor of MGC development.^{17,18} In multivariate analysis, *H. pylori* infection, mucosal atrophy, and intestinal metaplasia of index cases were not different between re-ESD and surgery group (Table 2). *H. pylori* infection triggers precancerous lesions such as atro-

phic gastritis and intestinal metaplasia. The carcinogenesis from precancerous lesions may progress by cellular adaptive mechanisms including endoplasmic reticulum stress, unfolded protein response, autophagy, oxidative stress, inflammation, epithelial-to-mesenchymal transition regardless of persistent *H. pylori* infection.¹⁹⁻²³ The result that *H. pylori* infection in index cases was not associated with the decision of treatment strategy of MGC in this study may suggest that these cascade and accumulation of epigenetic alteration might be more important in terms of invasiveness of MGC.

It has been well known that *H. pylori* eradication prevented MGC development.^{17,24,25} However, there were few studies about the relationship between persistent *H. pylori* infection and invasiveness of MGC. Although final status of *H. pylori* infection was unknown in some cases in this study and did not have statistical significance in the relationship with advanced MGC, persistent *H. pylori* infection tended to be more frequent in re-ESD group. Some studies have reported that *H. pylori* infection was more related to intestinal type gastric cancer than diffuse type,^{26,27} which implied that persistent *H. pylori* infection might be associated with re-ESD group rather than surgery group by slow tumor progression.

Multivariate analysis for the treatment outcome of MGC showed that depth of tumor invasion over mucosa, upper location of stomach, diffuse or mixed type were associated with surgery group. Diffuse or mixed type has been known to have aggressive characteristics such as LN spread. In a previous study, epithelial-to-mesenchymal transition-related tumors were generally diffuse type, which were usually diagnosed at advanced stage and had the worst prognosis.²⁸ On the other hand, undifferentiated histology was not related to MGC with high risk of LN metastasis. In a recent study, pure histology of poorly cohesive carcinoma showed higher risk of deeper tumor invasion and lymphovascular/perineural invasion than heterogenic histology.²⁹ In this study, heterogeneity of undifferentiated histology might not affect the invasiveness and treatment strategy of MGC.

MGC was more frequent in the upper third location in surgery than re-ESD group, where the tumor has been reported to be more invasive and have poorer prognosis.²⁹ Lymphovascular/perineural invasion was known as the indicators to poor prognosis of gastric cancer. A previous study has reported that gastric cancer with perineural invasion was associated with diffuse-mixed Lauren type and upper third location,³⁰ where tumor cells might easily spread out the gap between the large autonomic nerves and tissues.

The OS from treatment of MGC was significantly higher in re-ESD than surgery group. Mean follow-up duration of 24.8±19.5 months from the treatment for MGC was too short to compare disease free survival after MGC between the groups. Although we could only confirm OS of the groups, there was a the possibility that the gastric cancer-related death might be higher in the surgery group by significant higher mortality rate. Since

curative resection rate of re-ESD did not differ from surgery ($p>0.05$), the presence of LN metastasis might influence on prognosis of MGC.

This study has several limitations. As a single center retrospective study, there might be selection or information biases. Surgery group might show poor OS because MGC with high risk of LN metastasis was recommended to undergo surgical resection rather than re-ESD. Although exact LN metastasis in re-ESD group could not be evaluated without surgical evaluation including LN dissection, it might be postulated that higher OS was achieved during long-term follow-up without tumor recurrence from LN or distant metastasis in the re-ESD group in spite of similar rate of curative resection in both groups. *H. pylori* status was also unclear in many patients during follow-up. Although there was sufficient follow-up duration after index EGC, the number of MGC might be too small to evaluate the strong relationship between risk factors and MGC with LN metastasis.

In conclusion, lower BMI and multiplicity of index cancer were significantly related to subsequent MGC with high risk of LN metastasis. Close follow-up is mandatory for the patients with the risks to minimize the additional treatment for MGC after index ESD.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Data analysis and writing - original draft: J.L.K. Study design: H.C. Writing - review and editing: H.C., S.G.K. Advice on the study design: S.G.K. Statistical support and data acquisition: J.K., J.Y.P., H.J.Y., H.J.K. All authors have read and approved the manuscript.

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