Characteristics of metachronous gastric neoplasms after curative endoscopic submucosal dissection for early gastric neoplasms

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Abstract

Background: With the wide application of endoscopic submucosal dissection (ESD) for early gastric neoplasms, metachronous gastric neoplasms (MGN) have gradually become a concern. This study aimed to analyze the characteristics of MGN and evaluate the treatment and follow-up outcomes of MGN patients.

Methods: A total of 814 patients were retrospectively enrolled. All these patients were treated by ESD for early gastric cancer or gastric dysplasia between November 2006 and September 2019 at The First Medical Center of Chinese People's Liberation Army General Hospital. The risk factors for MGN were analyzed using Cox hazard proportional model. Moreover, the cumulative incidence, the correlation of initial lesions and MGN lesions, and the treatment and follow-up outcomes of MGN patients were analyzed.

Results: A total of 4.5% (37/814) of patients had MGN after curative ESD. The 3-, 5-, and 7-year cumulative incidences of MGN were 3.5%, 5.1%, and 6.9%, respectively, and ultimately reaching a plateau of 11.3% at 99 months after ESD. There was no significant correlation between initial lesions and MGN lesions in terms of gross type ($P = 0.178$), location (long axis: $P = 0.470$; short axis: $P = 0.125$), and histological type ($P = 0.832$). Cox multivariable analysis found that initial multiplicity was the only independent risk factor of MGN (hazard ratio: 4.3, 95% confidence interval: 2.0–9.4, $P < 0.001$). Seventy-three percent of patients with MGN were treated by endoscopic resection. During follow-up, two patients with MGN died of gastric cancer with lymph node metastasis. The disease-specific survival rate was significantly lower in patients with MGN than that in patients without MGN (94.6% *vs.* 99.6%, $P = 0.006$).

Conclusions: The MGN rate gradually increased with follow-up time within 99 months after curative gastric ESD. Thus, regular and long-term surveillance endoscopy may be helpful, especially for patients with initial multiple neoplasms.

Keywords: Metachronous gastric neoplasms; Early gastric cancer; Endoscopic submucosal dissection; Characteristics; Follow-up

Introduction

Endoscopic submucosal dissection (ESD) has become the main treatment for early gastric cancer (EGC) with no risk of lymph node metastasis, regardless of lesion size or presence of ulcers.[1,2] Compared with radical gastrectomy, ESD can preserve intact organs and provide a better life quality after ESD.[3,4] However, the incidence of metachronous gastric neoplasms (MGN) after ESD is higher than that after radical gastrectomy. According to previous studies, the MGN rate after ESD was 2.7% to 15.6%,[5,6] while the rate after surgery ranged from 0.1% to 3.0%.[7-9] Therefore, MGN have become a concern for EGC patients treated with ESD.

Previous studies have analyzed potential risk factors for MGN,[6,10-17] such as advanced age, male sex, initial multiplicity, intestinal metaplasia, severe gastric atrophy, and *Helicobacter pylori* (*H. pylori*) infection. However, the samples of some studies were small,[10,11,13] and some studies did not distinguish MGN from synchronous gastric cancer or local recurrence.[13,17]

Because of the minimal invasiveness of ESD and its ability to resect large lesions in one piece, many patients prefer ESD to surgery. It is well known that the therapeutic effect of ESD is closely related to the time of diagnosis and treatment. Therefore, the early detection and diagnosis of MGN are essential. Besides, it is necessary for MGN patients to follow up regularly and understand the outcome of ESD in the treatment of MGN.

This study had two primary purposes: (1) to analyze the characteristics of MGN, including its incidence rate and

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relevant risk factors, and (2) to evaluate the treatment and follow-up outcomes of MGN patients.

Methods

Patients and ethical approval

Totally 1361 patients with EGC or gastric dysplasia were retrospectively included in this study. All included patients were treated with ESD when the absolute and expanded criteria of ESD were met according to the Japanese Gastric Cancer Treatment Guidelines[2] from November 2006 to September 2019 at The First Medical Center of Chinese People's Liberation Army (PLA) General Hospital. Before ESD, all patients signed informed consent. The exclusion criteria were (1) ESD after subtotal gastrectomy; (2) non-curative resection, which was based on histological criteria; (3) additional surgery after ESD; (4) a follow-up period <1 year or follow-up loss; (5) local recurrence or occurrence of synchronous gastric neoplasms after ESD. Finally, medical records, endoscopic records, and pathological results were collected. The flowchart of this study was shown in Figure 1. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[18,19] and conducted in accordance with the *Declaration of Helsinki* and was approved by the local Ethics Committee of The First Medical Center of Chinese PLA General Hospital (No. S2017-010-02).

Follow-up

Endoscopic surveillance was recommended at 3, 6, and 12 months after ESD, followed by annual or biannual gastroscopy. Tumor markers, computed tomography, ultrasound, and other related examinations were also performed as necessary. Endoscopic resection (ER) was recommended for patients with MGN when the absolute and expanded criteria of ER were met according to the Japanese Gastric Cancer Treatment Guidelines.[2] Resected specimens were fixed entirely on a plate to stretch the specimen fully and then fixed in 10% neutral formalin. Histological evaluation was performed after the specimens were serially sectioned at specific intervals. The histological type, lesion size, invasion depth, lymphovascular involvement, and margin status were assessed.

Patients who were unable to come to the hospital for gastroscopy on time for various reasons were followed up by telephones, and their endoscopic follow-up or re-treatment records were obtained by email, WeChat, or multimedia messaging service (MMS). The follow-up information for these cases included whether additional surgery or gastroscopy had been performed after ESD, the time of gastroscopy, whether MGN was found and treated, how it was treated, and postoperative pathology results. Follow-up time refers to the interval between the initial ESD and the date of death or March 31, 2020.

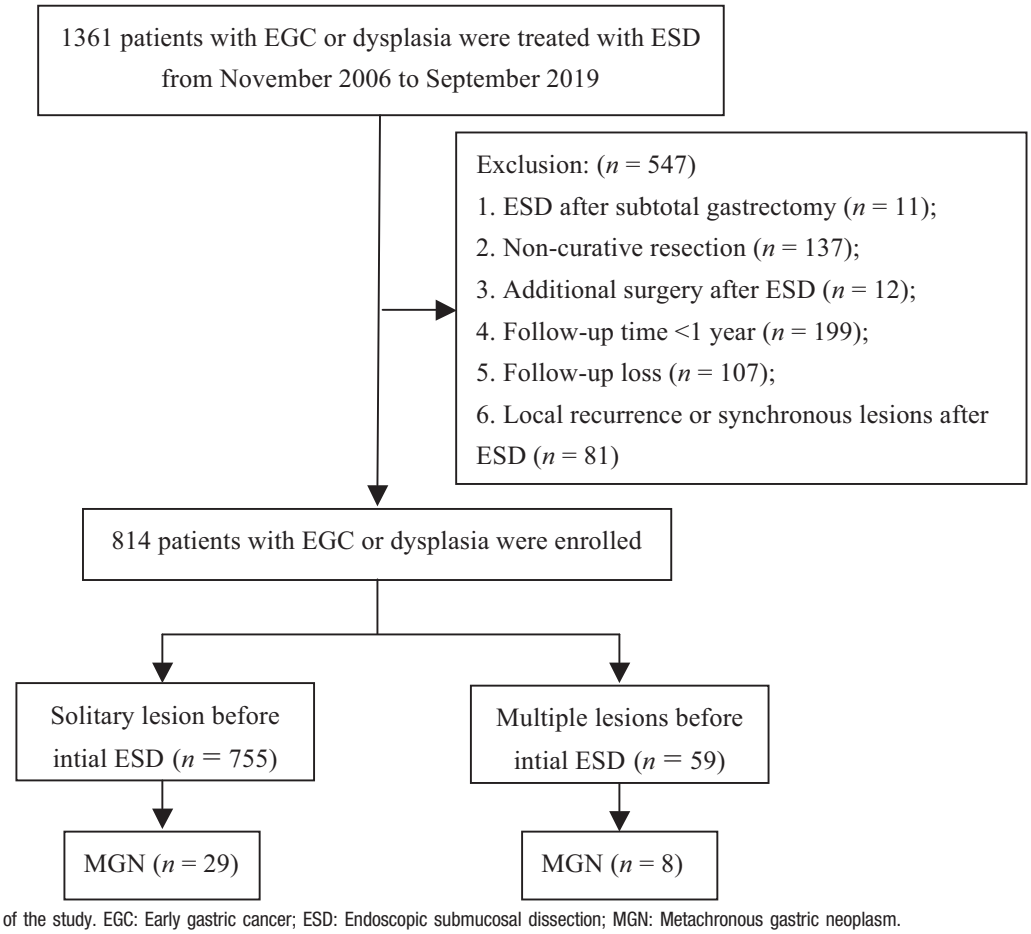

Figure 1: Flowchart of the study. EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; MGN: Metachronous gastric neoplasm.

Definitions

MGN indicates a new neoplasm found at least 12 months after initial ESD treatment, ≥1 cm from the initial lesion.[20] Lesion location was divided along the long axis into upper (cardia, gastric fundus, and upper part of the gastric body), middle (middle and the lower parts of the gastric body, and the angle), and lower (antrum and pylorus). Lesion location along the short axis was classified as lesser curvature, anterior wall, greater curvature, and posterior wall.[21] According to the Paris classification,[22] gastric lesions were classified macroscopically, as elevated, flat, and depressed.

H. pylori infection status was determined by two biopsy-based tests (a histology test and a rapid urease test) and a ^{13}C urea breath test. The biopsy site included the lesser curvature of the gastric antrum and body. Giemsa staining was used for a histological evaluation of *H. pylori* infection. At least one of these three tests was performed on each patient, and a positive result from any of these tests was regarded as positive for *H. pylori* infection. For patients with *H. pylori* infection, a 2-week quadruple drug eradication therapy (two antibiotics, one proton pump inhibitor, and one bismuth agent) was recommended. Then, the ^{13}C urea breath test was performed 4 weeks after the eradication therapy had been stopped to determine whether the therapy was successful. The diagnosis of atrophic gastritis was confirmed using the Kimura–Takemoto classification,[23] severe atrophy including type O-2 and type O-3 according to this classification. The presence of intestinal metaplasia was evaluated by endoscopic examination.[24]

En bloc resection indicated that the lesions were resected under an endoscope as a single piece. Complete resection referred to the *en bloc* resection in which the horizontal and vertical margins were negative. Curative resection was defined as complete resection without lymphovascular involvement and/or with negligible risk of regional lymph node metastasis. Disease-specific survival meant the interval from the initial ESD to the last follow-up or death due to gastric cancer.

Statistical analysis

Continuous variables with normal distribution were presented as the mean ± standard deviation, while variables with abnormal distribution were presented as the median and interquartile range (IQR), and analyzed by the Student's *t* test or Mann-Whitney *U* test. Categorical variables were presented as numbers (percentage) and analyzed by the χ^2 test or the Fisher exact test. The correlation between initial lesions and MGN lesions was analyzed using the method of cascading correlation analysis. The variables with *P* value <0.100 in the univariate analysis were included in the Cox hazard proportional model for multivariable analysis. A *P* value <0.050 was considered to be statistically significant. Data were analyzed using the statistical packages R (version 3.4.3) and Empower (R) (Boston, MA, USA).

Results

Patients' characteristics

Among the 1361 patients, 547 were excluded for the following reasons: (1) ESD after subtotal gastrectomy, 11 patients; (2) non-curative resection, 137 patients; (3) additional surgery after ESD, 12 patients; (4) follow-up period <1 year, 199 patients; (5) follow-up loss, 107 patients; and (6) local recurrence or occurrence of synchronous gastric neoplasms after ESD, 81 patients. Finally, 814 patients were enrolled in this study, including 37 patients who had MGN after ESD over a median follow-up time of 40.5 (12–146) months. Thus, the incidence of MGN in this study was 4.5% (37/814). Among the 37 patients with MGN, 33 had only one MGN, while the other four patients had two MGNs. Details of these cases are as follows: one patient had two MGNs 25 months after initial ESD; one patient had two MGNs 72 months after initial ESD; one patient had one MGN 86 months after initial ESD and another MGN 30 months after the second ESD; one patient had one MGN 73 months after initial ESD and another MGN 25 months after the second ESD.

The median age (IQR) of all 814 patients was 60.0 (53.0–68.0) years and 76.4% (622/814) were males. Among all patients, 38.6% and 38.2% had a history of smoking and drinking alcohol, respectively, and 173 (21.3%) patients had a family history of gastric cancer. Besides, 518 (63.6%) patients had severe gastric atrophy and 638 (78.4%) patients had intestinal metaplasia. A total of 77.3% (597/814) of the lesions were elevated. Most of the lesions were located in the lower third of the stomach (44.7%), followed by the upper third (32.6%) and the middle third of the stomach (22.7%). Regarding histology, 34.2% (278/814), 4.5% (37/814), and 61.3% (499/814) of the lesions were differentiated carcinoma, undifferentiated carcinoma, and dysplasia, respectively. A total of 95.3% (776/814) of the lesions were limited to the mucosa layer. Finally, 59 (7.2%) patients had multiple lesions at the time of initial ESD.

Characteristics of MGN

The median (IQR) lesion size of initial lesions and MGN lesions were 1.1 (0.7–1.8) cm and 1.5 (0.9–2.5) cm, respectively. This difference was not statistically significant ($P = 0.133$) [Supplementary Figure 1, http://links.lww.com/CM9/A761].

The correlation between initial lesions and MGN lesions is shown in Table 1. Most of the initial lesions (86.5%) and MGN lesions (64.9%) were elevated. When the initial lesions were elevated type, 71.9% of MGN lesions were also elevated type. The most common location (long axis) of initial lesions and MGN lesions was the lower third of the stomach (56.8% *vs.* 37.8%), followed by the middle third (24.3% *vs.* 32.4%) and upper third of the stomach (18.9% *vs.* 29.7%). As for the short axis of the stomach, lesser curvature was the most common location of both initial lesions and MGN lesions. According to histological

Table 1: Correlation between initial lesions and MGN lesions ($N = 37$).

Initial lesions → MGN lesions	Values	χ^2	*P*
Gross type		6.305	0.178
Elevated → E/F/D	32 → 23/6/3		
Flat → E/F/D	2 → 0/1/1		
Depressed → E/F/D	3 → 1/1/1		
Location (long axis)		3.554	0.470
Upper 1/3 → U/M/L	7 → 3/1/3		
Middle 1/3 → U/M/L	9 → 4/3/2		
Lower 1/3 → U/M/L	21 → 4/8/9		
Location (short axis)		13.935	0.125
LC → LC/AW/GC/PW	19 → 7/0/4/8		
AW → LC/AW/GC/PW	9 → 3/3/1/2		
GC → LC/AW/GC/PW	2 → 0/0/1/1		
PW → LC/AW/GC/PW	7 → 4/0/2/1		
Histology		5.030	0.832
D-CA → D-CA/UD-CA/HGIN/LGIN	11 → 3/2/4/2		
UD-CA → D-CA/UD-CA/HGIN/LGIN	3 → 1/1/0/1		
HGIN → D-CA/UD-CA/HGIN/LGIN	18 → 8/1/5/4		
LGIN → D-CA/UD-CA/HGIN/LGIN	5 → 2/0/2/1		

Values were shown as *n*. AW: Anterior wall; D-CA: Differentiated carcinoma; E/F/D: Elevated/flat/depressed; GC: Greater curvature; HGIN: High-grade intraepithelial neoplasia; LC: Lesser curvature; LGIN: Low-grade intraepithelial neoplasia; MGN: Metachronous gastric neoplasm; PW: Posterior wall; U/M/L: Upper/middle/lower 1/3; UD-CA: Undifferentiated carcinoma.

findings, most MGN lesions (37.8%) were differentiated cancer, while high-grade intraepithelial neoplasia (48.6%) was most common among initial lesions. However, there was no significant correlation between initial lesions and MGN lesions in terms of gross type ($P = 0.178$), location (long axis: $P = 0.470$; short axis: $P = 0.125$), and histological type ($P = 0.832$) of the lesions.

In the univariate analysis, both the rate of severe gastric atrophy (83.8% *vs.* 62.7%, $P = 0.003$) and initial multiplicity (21.6% *vs.* 6.6%, $P = 0.001$) were significantly higher in patients with MGN than those in patients without MGN, while the percentage of patients who received *H. pylori* eradication was lower among MGN patients than among those without MGN (10.8% *vs.* 16.3%, $P = 0.097$). However, multivariate analysis showed that only initial multiplicity (hazard ratio [HR]: 4.3, 95% confidence interval [CI]: 2.0–9.4, $P < 0.001$) was an independent risk factor of MGN [Table 2].

The average interval between the date of initial ESD and the date when MGN was diagnosed was 42.6 months (range: 13–99 months). The 3-, 5-, and 7-year cumulative incidences of MGN (CIMGN) were 3.5%, 5.1%, and 6.9%, respectively, and it reached a plateau of 11.3% at 99 months after ESD [Figure 2].

Treatment and follow-up of patients with MGN

Figure 3 shows the treatment methods and therapeutic outcomes of patients with MGN. Among the 37 patients with MGN, two were treated with surgery. One such patient was a 75-year-old man, whose pathology of surgery was mucinous adenocarcinoma that had invaded the submucosal layer, he finally died of lymph node metastasis 23 months after surgery. The other patient who underwent surgery was a 72-year-old female patient; her pathology of surgery was poorly differentiated adenocarcinoma that had invaded the deep muscle layer. She received radiotherapy after surgery and was followed up for 86 months. She was still alive at the last follow-up date.

In total, 27 patients with MGN (73%) received ER, including 26 ESD and one cutting-endoscopic mucosal resection. The *en bloc* resection rate, complete resection rate, and curative resection rate were 96% (26/27), 89% (24/27), and 82% (22/27), respectively (data not shown). The reasons for the five patients who failed to achieve curative resection were positive margin (two patients), piece resection (one patient), and lymphovascular infiltration (two patients). Two patients with positive margins received re-ESD 9 months after ESD for MGN. A 66-year-old male patient underwent piece resection because of severe adhesion, he did not undergo regular endoscopy 10 months after ESD for MGN, and finally died of gastric cancer with lymph node metastasis 54 months later. The other two patients with lymphovascular infiltration did not undergo additional treatment before the last follow-up date. Of the remaining eight patients who did not receive surgery and ER, one underwent chemotherapy (the pathology of the metachronous lesion was poorly differentiated adenocarcinoma), one received photodynamic therapy (the pathology of the metachronous lesion was local cancer), five underwent radiofrequency ablation (the pathology of the metachronous lesions were low-grade intraepithelial neoplasia), and one did not receive any treatment. The eight patients were all alive at the last date of follow-up.

Among all 814 included patients, 23 died, including 21 patients without MGN, among which two patients died of gastric cancer, while both two patients with MGN died of gastric cancer. The overall survival rate of patients with and without MGN were 94.6% and 97.3% ($P = 0.893$),

Table 2: Univariable analysis and multivariable analysis of risk factors for MGN after curative ESD for EGC.

Variables	Patients without MGN ($n = 777$)	Patients with MGN ($n = 37$)	Statistics	P	Multivariate analysis HR (95% CI)	P
Age (years), median (IQR)	60.0 (53.0–68.0)	63.0 (55.0–70.5)	−1.616*	0.106		
≥65 years, *n* (%)	268 (34.5)	16 (43.2)	1.191†	0.434		
Gender (male), *n* (%)	592 (76.2)	30 (81.1)	0.469†	0.473		
BMI (kg/m^2), median (IQR)	24.4 (22.1–26.6)	24.2 (22.3–25.0)	−1.059*	0.289		
H. pylori infection, *n* (%)	318 (40.9)	22 (59.5)	4.987†	0.821		
H. pylori eradication, *n* (%)	127 (16.3)	4 (10.8)	0.801†	0.097	1.5 (0.7–3.2)	0.297
Smoking, *n* (%)	297 (38.2)	17 (45.9)	0.889†	0.346		
Drinking alcohol, *n* (%)	295 (38.0)	17 (45.9)	0.951†	0.329		
Family history of GC, *n* (%)	168 (21.6)	5 (13.5)	1.387†	0.433		
Severe gastric atrophy, *n* (%)	487 (62.7)	31 (83.8)	6.799†	0.003	2.0 (0.8–5.2)	0.166
Intestinal metaplasia, *n* (%)	606 (78.0)	32 (86.5)	1.504†	0.220		
Lesion size (cm), median (IQR)	1.1 (0.7–1.8)	1.5 (0.8–2.0)	−0.011*	0.718		
Gross type, *n*			3.428†	0.315		
Elevated/flat/depressed	565/88/124	32/2/3				
Location (long axis), *n*			3.514†	0.173		
Upper/middle/lower	258/176/343	7/9/21				
Histology, *n*			1.309†	0.566		
D-CA/UD-CA/GD	267/34/476	11/3/23				
Invasion depth (M/SM), *n*	742/35	34/3	1.031†	0.310		
Initial multiplicity, *n* (%)	51 (6.6)	8 (21.6)	11.912†	0.001	4.3 (2.0–9.4)	<0.001

*Z values. †χ^2 values. BMI: Body mass index; CI: Confidence interval; D-CA: Differentiated carcinoma; EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; GC: Gastric cancer; HR: Hazard ratio; IQR: Interquartile range; M: Mucosa; MGN: Metachronous gastric neoplasm; SM: Submucosa; UD-CA: Undifferentiated carcinoma; GD: Gastric dysplasia.

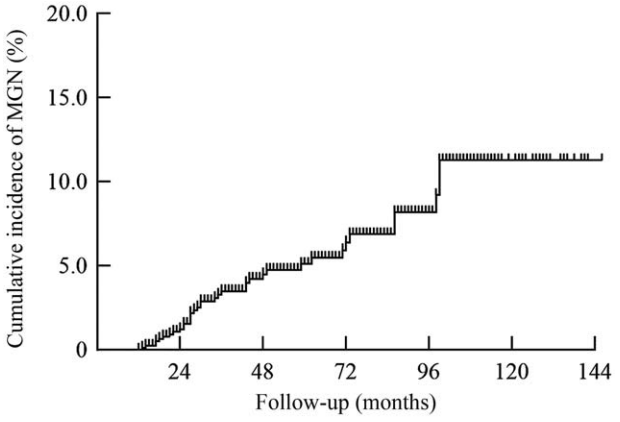

Figure 2: The cumulative incidence of MGN after curative endoscopic submucosal dissection for gastric neoplastic lesions. MGN: Metachronous gastric neoplasm.

respectively, but the disease-specific survival rate was significantly lower in patients with MGN (94.6% *vs.* 99.6%, $P = 0.006$) [Figure 4].

Discussion

In this study, we found that the incidence of MGN was 4.5% and the CIMGN increased gradually with the prolonged follow-up time, which reached a plateau of 11.3% at 99 months after ESD. Most of the MGN lesions were differentiated intramucosal carcinoma and dysplasia, 64.9% of the MGN lesions were elevated, and 70.2% were located in the middle and lower parts of the stomach. Multivariate analysis showed initial multiplicity was an independent risk factor for MGN. Among the 37 patients with MGN, 27 patients (73.0%) received ER, two patients died of lymph node metastasis, and the disease-specific survival rate was significantly lower in patients with MGN than that in patients without MGN. These results are useful for improving the detection rate of MGN and formulating individualized follow-up strategies for ESD patients.

Previous studies found that most of the MGN lesions were differentiated intramucosal carcinoma and dysplasia. Moreover, MGN usually occurs when the initial lesion is differentiated carcinoma or dysplasia.[10,23,25-27] Our study was consistent with these studies. These results may be explained by the "field cancerization" theory.[28,29] Besides, in this study, 27 (73.0%) of the included MGN patients were treated with ER, of which 81.5% received curative resection. In the study conducted by Abe *et al*,[6] 90.3% of patients with MGN were treated with ER, and the curative resection rate was 88.8%. Our study showed that surveillance endoscopy can detect MGNs at an early stage so that they can be treated with minimally invasive ER to preserve intact stomach, prevent early MGNs from developing into advanced cancers, and deprive patients of the opportunity for early diagnosis and early treatment.

There are some guidelines on follow-up strategies for patients who achieved curative ER for EGC. According to the National Comprehensive Cancer Network guidelines, even patients with carcinoma *in situ* (Tis) or stage T1 stage gastric cancer without lymph node metastasis who have achieved complete resection during ER or surgery should receive regular follow-ups at intervals of every 3 to

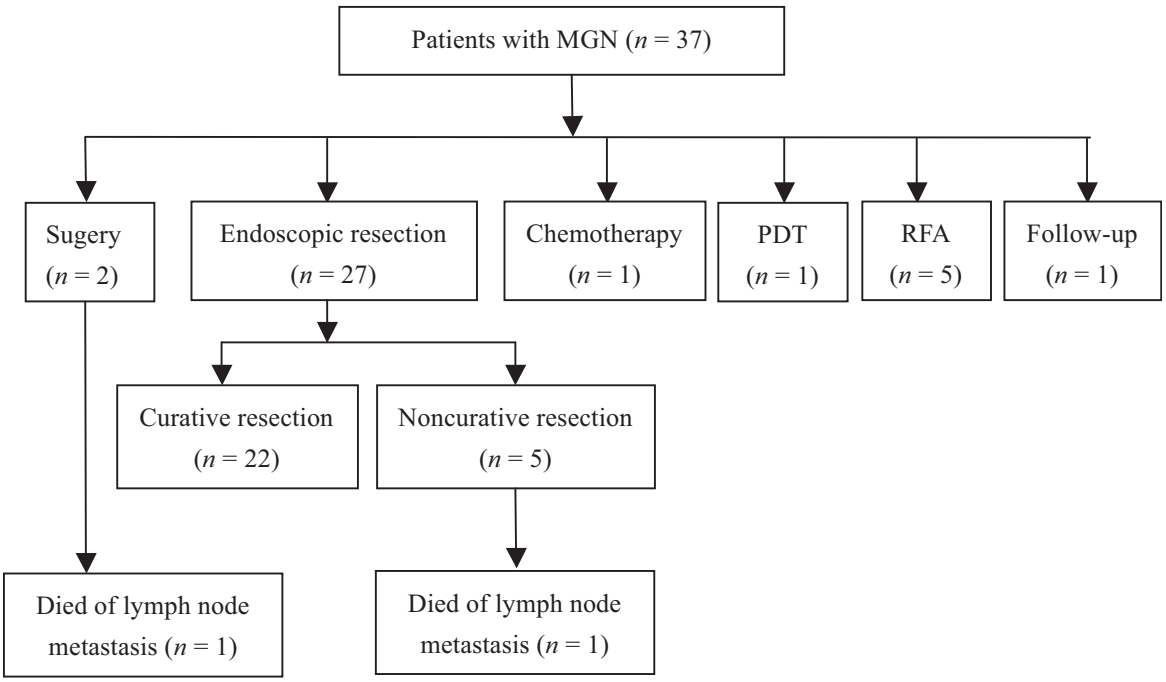

Figure 3: The treatment and outcomes of patients with MGN after curative endoscopic submucosal dissection for gastric neoplastic lesions. MGN: Metachronous gastric neoplasm; PDT: Photodynamic therapy; RFA: Radiofrequency ablation.

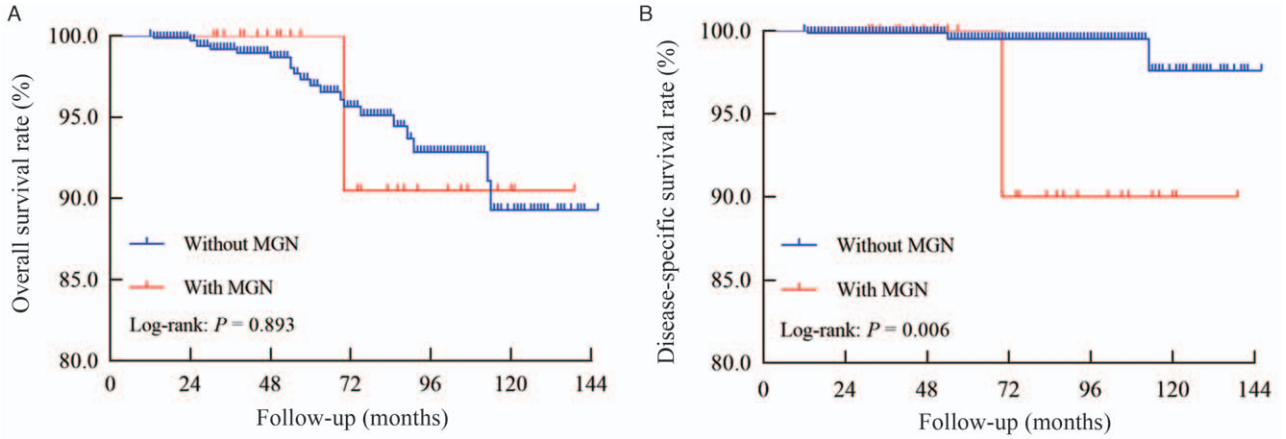

Figure 4: Comparison of survival rate between patients with MGN and patients without MGN. (A) Overall survival rate, (B) disease-specific survival rate. MGN: Metachronous gastric neoplasm.

6 months for the first 1 to 2 years after ESD, then every 6 to 12 months for the following 3 to 5 years, and annually thereafter.[30] For patients with EGC who underwent curative resection, the Japanese guidelines for the treatment of EGC recommend that endoscopic follow-up should be conducted at 3, 6, and 12 months after ESD, followed by annual or biannual endoscopy.[31,32] Kato *et al*[23] proposed an annual follow-up for at least 5 years after ER based on the results of a multicenter cohort study. However, our study found that the CIMGN increased with follow-up time and reached a plateau 99 months after ESD. Kobayashi *et al*[10] also had similar findings. Therefore, we recommend that endoscopic follow-up be longer, such as 10 years, especially for patients with initial multiple neoplasms.

Gastric adenocarcinoma development following *H. pylori* infection progresses from chronic active gastritis, atrophic gastritis, intestinal metaplasia, gastric dysplasia, and finally to gastric adenocarcinoma. Thus, *H. pylor*i infection is one of the most important risk factors for gastric cancer.[5] However, it is controversial whether *H. pylori* infection and its eradication affect the incidence of MGN. Some studies have found that *H. pylori* eradication can reduce the incidence of MGN. For example, a study conducted by Nakata *et al*[33] using the method of propensity matching showed that successful eradication of *H. pylori* could significantly decrease the incidence of MGN after ESD for EGC; Zhao *et al*[34] conducted a meta-analysis and found that successful *H. pylori* eradication can significantly reduce the incidence of MGN (HR: 0.65,

95% CI: 0.50–0.86, $P = 0.002$). However, other studies have found that *H. pylori* status has no significant effect on the development of MGN.[12,35,36] Our study also found that *H. pylori* infection and eradication were not significantly related to MGN. The effects of *H. pylori* on the incidence of MGN may be related to the time between ESD and *H. pylori* infection or eradication, but many previous studies and this study have not clarified the effects of these variables. In the future, prospective, large-scale, multicenter studies with long-term follow-up will be needed to further clarify the impact of *H. pylori* status on the incidence of MGN and to stratify the risk factors for MGN. Understanding these variables will help guide clinicians to formulate individualized surveillance strategies for patients.

There were a few limitations to this study. First, it was a single-center, retrospective study. Second, some patients did not have regular endoscopic surveillance at our hospital for various reasons. Their conditions were only known by telephone follow-up, limiting our ability to view their entire medical records, endoscopic records, and detailed information about MGN.

In conclusion, initial multiplicity was an independent risk factor for MGN after ESD for gastric neoplasms. There was no significant correlation between initial lesions and MGN lesions in terms of gross type, lesion location, and histological type of lesions. The CIMGN increased gradually with the follow-up time, so regular and long-term follow-up should be performed even for EGC patients who have undergone curative ER, especially for patients with initial multiplicity. In the future, prospective, large sample, multicenter studies are warranted to verify our conclusions further.

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Conflicts of interest

None.

References

1. Lee JH, Kim JG, Jung HK, Kim JH, Jeong WK, Jeon TJ, *et al*. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. J Gastric Cancer 2014;14:87–104. doi: 10.5230/jgc.2014.14.2.87.
2. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1–21. doi: 10.1007/s10120-020-01042-y.
3. Tae CH, Shim KN, Kim BW, Kim JH, Hong SJ, Baik GH, *et al*. Comparison of subjective quality of life after endoscopic submucosal resection or surgery for early gastric cancer. Sci Rep 2020;10:6680. doi: 10.1038/s41598-020-62854-7.
4. An L, Gaowa S, Cheng H, Hou M. Long-term outcomes comparison of endoscopic resection with gastrectomy for treatment of early gastric cancer: a systematic review and meta-analysis. Front Oncol 2019;9:725. doi: 10.3389/fonc.2019.00725.
5. Abe S, Oda I, Minagawa T, Sekiguchi M, Nonaka S, Suzuki H, *et al*. Metachronous gastric cancer following curative endoscopic resection of early gastric cancer. Clin Endosc 2018;51:253–259. doi: 10.5946/ce.2017.104.
6. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Nakajima T, *et al*. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy 2015;47:1113–1118. doi: 10.1055/s-0034-1392484.
7. Iwata Y, Ito S, Misawa K, Ito Y, Komori K, Abe T, *et al*. Incidence and treatment of metachronous gastric cancer after proximal gastrectomy. Surg Today 2018;48:552–557. doi: 10.1007/s00595-018-1632-0.
8. Kinami S, Aizawa M, Yamashita H, Kumagai K, Kamiya S, Toda M, *et al*. The incidences of metachronous multiple gastric cancer after various types of gastrectomy: analysis of data from a nationwide Japanese survey. Gastric Cancer 2021;24:22–30. doi: 10.1007/s10120-020-01104-1.
9. Onodera H, Tokunaga A, Yoshiyuki T, Kiyama T, Kato S, Matsukura N, *et al*. Surgical outcome of 483 patients with early gastric cancer: prognosis, postoperative morbidity and mortality, and gastric remnant cancer. Hepatogastroenterology 2004;51:82–85. doi: 10.1532/HSF98.20040001.
10. Kobayashi M, Narisawa R, Sato Y, Takeuchi M, Aoyagi Y. Self-limiting risk of metachronous gastric cancers after endoscopic resection. Dig Endosc 2010;22:169–173. doi: 10.1111/j.1443-1661.2010.00987.x.
11. Han JS, Jang JS, Choi SR, Kwon HC, Kim MC, Jeong JS, *et al*. A study of metachronous cancer after endoscopic resection of early gastric cancer. Scand J Gastroenterol 2011;46:1099–1104. doi: 10.3109/00365521.2011.591427.
12. Maehata Y, Nakamura S, Fujisawa K, Esaki M, Moriyama T, Asano K, *et al*. Long-term effect of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. Gastrointest Endosc 2012;75:39–46. doi: 10.1016/j.gie.2011.08.030.
13. Jang MY, Cho JW, Oh WG, Ko SJ, Han SH, Baek HK, *et al*. Clinicopathological characteristics of synchronous and metachronous gastric neoplasms after endoscopic submucosal dissection. Korean J Intern Med 2013;28:687–693. doi: 10.3904/kjim.2013.28.6.687.
14. Kim YI, Choi IJ, Kook MC, Cho SJ, Lee JY, Kim CG, *et al*. The association between Helicobacter pylori status and incidence of metachronous gastric cancer after endoscopic resection of early gastric cancer. Helicobacter 2014;19:194–201. doi: 10.1111/hel.12116.
15. Kwon YH, Heo J, Lee HS, Cho CM, Jeon SW. Failure of Helicobacter pylori eradication and age are independent risk factors for recurrent neoplasia after endoscopic resection of early gastric cancer in 283 patients. Aliment Pharmacol Ther 2014;39:609–618. doi: 10.1111/apt.12633.
16. Min BH, Kim ER, Kim KM, Park CK, Lee JH, Rhee PL, *et al*. Surveillance strategy based on the incidence and patterns of recurrence after curative endoscopic submucosal dissection for early gastric cancer. Endoscopy 2015;47:784–793. doi: 10.1055/s-0034-1392249.
17. Moon HS, Yun GY, Kim JS, Eun HS, Kang SH, Sung JK, *et al*. Risk factors for metachronous gastric carcinoma development after endoscopic resection of gastric dysplasia: retrospective, single-center study. World J Gastroenterol 2017;23:4407–4415. doi: 10.3748/wjg.v23.i24.4407.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4:e296. doi: 10.1371/journal.pmed.0040296.
19. Cuschieri S. The STROBE guidelines. Saudi J Anaesth 2019;13:S31–S34. doi: 10.4103/sja.SJA_543_18.
20. Lee HJ, Lee YJ, Lee JY, Kim ES, Chung WJ, Jang BK, *et al*. Characteristics of synchronous and metachronous multiple gastric tumors after endoscopic submucosal dissection of early gastric neoplasm. Clin Endosc 2018;51:266–273. doi: 10.5946/ce.2017.109.
21. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101–112. doi: 10.1007/s10120-011-0041-5.
22. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3–S43. doi: 10.1016/s0016-5107(03)02159-x.

23. Kato M, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, *et al*. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. Gut 2013;62:1425–1432. doi: 10.1136/gutjnl-2011-301647.
24. Fukuta N, Ida K, Kato T, Uedo N, Ando T, Watanabe H, *et al*. Endoscopic diagnosis of gastric intestinal metaplasia: a prospective multicenter study. Dig Endosc 2013;25:526–534. doi: 10.1111/den.12032.
25. Hosokawa O, Kaizaki Y, Watanabe K, Hattori M, Douden K, Hayashi H, *et al*. Endoscopic surveillance for gastric remnant cancer after early cancer surgery. Endoscopy 2002;34:469–473. doi: 10.1055/s-2002-32007.
26. Nakajima T, Oda I, Gotoda T, Hamanaka H, Eguchi T, Yokoi C, *et al*. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? Gastric Cancer 2006;9:93–98. doi: 10.1007/s10120-006-0372-9.
27. Nozaki I, Hato S, Kobatake T, Ohta K, Kubo Y, Nishimura R, *et al*. Incidence of metachronous gastric cancer in the remnant stomach after synchronous multiple cancer surgery. Gastric Cancer 2014;17:61–66. doi: 10.1007/s10120-013-0261-y.
28. McDonald SAC, Greaves LC, Gutierrez-Gonzalez L, Rodriguez-Justo M, Deheragoda M, Leedham SJ, *et al*. Mechanisms of field cancerization in the human stomach: the expansion and spread of mutated gastric stem cells. Gastroenterology 2008;134:500–510. doi: 10.1053/j.gastro.2007.11.035.
29. Willenbrink TJ, Ruiz ES, Cornejo CM, Schmults CD, Arron ST, Jambusaria-Pahlajani A. Field cancerization: definition, epidemiology, risk factors, and outcomes. J Am Acad Dermatol 2020;83:709–717. doi: 10.1016/j.jaad.2020.03.126.
30. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, *et al*. Gastric cancer, version 3.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016;14:1286–1312. doi: 10.6004/jnccn.2016.0137.
31. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1–19. doi: 10.1007/s10120-016-0622-4.
32. Ono H, Yao K, Fujishiro M, Oda I, Nimura S, Yahagi N, *et al*. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc 2016;28:3–15. doi: 10.1111/den.12518.
33. Nakata R, Nagami Y, Hashimoto A, Sakai T, Ominami M, Fukunaga S, *et al*. Successful eradication of Helicobacter pylori could prevent metachronous gastric cancer: a propensity matching analysis. Digestion 2021;102:236–245. doi: 10.1159/000504132.
34. Zhao B, Zhang J, Mei D, Luo R, Lu H, Xu H, *et al*. Does Helicobacter pylori eradication reduce the incidence of metachronous gastric cancer after curative endoscopic resection of early gastric cancer: a systematic review and meta-analysis. J Clin Gastroenterol 2020;54:235–241. doi: 10.1097/mcg.0000000000001195.
35. Kim SB, Lee SH, Bae SI, Jeong YH, Sohn SH, Kim KO, *et al*. Association between Helicobacter pylori status and metachronous gastric cancer after endoscopic resection. World J Gastroenterol 2016;22:9794–9802. doi: 10.3748/wjg.v22.i44.9794.
36. Choi J, Kim SG, Yoon H, Im JP, Kim JS, Kim WH, *et al*. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol 2014;12:793–800.e1. doi: 10.1016/j.cgh.2013.09.057.

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