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 small13,16 and some studies did not distinguish MGN from synchronous gastric cancer or local recurrence.11,17

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
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 retreatment 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.

<table>
<thead>
<tr>
<th>1361 patients with EGC or dysplasia were treated with ESD from November 2006 to September 2019</th>
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<tbody>
<tr>
<td>Exclusion: (n = 547)</td>
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<tr>
<td>1. ESD after subtotal gastrectomy (n = 11);</td>
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<tr>
<td>2. Non-curative resection (n = 137);</td>
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<td>3. Additional surgery after ESD (n = 12);</td>
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<td>4. Follow-up time &lt; 1 year (n = 199);</td>
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<td>5. Follow-up loss (n = 107);</td>
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<tr>
<td>6. Local recurrence or synchronous lesions after ESD (n = 81)</td>
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<td>814 patients with EGC or dysplasia were enrolled</td>
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<tr>
<td>Solitary lesion before initial ESD (n = 755)</td>
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<tr>
<td>MGN (n = 29)</td>
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<tr>
<td>Multiple lesions before initial ESD (n = 59)</td>
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<td>MGN (n = 8)</td>
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</table>

*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. 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. According to the Paris classification, 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 13C 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 13C 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–Take-moto classification, severe atrophy including type O-2 and type O-3 according to this classification. The presence of intestinal metaplasia was evaluated by endoscopic examination.

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 χ² 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-curate 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 (86.3%) 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
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).

**Treatmen**t 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% ($P = 0.893$), respectively.
Table 2: Univariable analysis and multivariable analysis of risk factors for MGN after curative ESD for EGC.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients without MGN (n = 777)</th>
<th>Patients with MGN (n = 37)</th>
<th>Statistics</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>60.0 (53.0–68.0)</td>
<td>63.0 (55.0–70.5)</td>
<td>−1.616†</td>
<td>0.106</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>268 (34.5)</td>
<td>16 (43.2)</td>
<td>1.191‡</td>
<td>0.434</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>592 (76.2)</td>
<td>30 (81.1)</td>
<td>0.469†</td>
<td>0.473</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>24.4 (22.1–26.6)</td>
<td>24.2 (22.3–25.0)</td>
<td>−1.059§</td>
<td>0.289</td>
</tr>
<tr>
<td>H. pylori infection, n (%)</td>
<td>318 (40.9)</td>
<td>22 (59.5)</td>
<td>4.987‡</td>
<td>0.821</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>127 (16.3)</td>
<td>4 (10.8)</td>
<td>0.801†</td>
<td>0.907</td>
</tr>
<tr>
<td>Drinking alcohol, n (%)</td>
<td>297 (38.2)</td>
<td>17 (45.9)</td>
<td>0.889†</td>
<td>0.346</td>
</tr>
<tr>
<td>Family history of GC, n (%)</td>
<td>168 (21.6)</td>
<td>5 (13.5)</td>
<td>1.387†</td>
<td>0.433</td>
</tr>
<tr>
<td>Severe gastric atrophy, n (%)</td>
<td>487 (62.7)</td>
<td>31 (83.8)</td>
<td>6.799†</td>
<td>0.003</td>
</tr>
<tr>
<td>Intestinal metaplasia, n (%)</td>
<td>606 (78.0)</td>
<td>32 (86.5)</td>
<td>1.504†</td>
<td>0.220</td>
</tr>
<tr>
<td>Lesion size (cm), median (IQR)</td>
<td>1.1 (0.7–1.8)</td>
<td>1.5 (0.8–2.0)</td>
<td>−0.011†</td>
<td>0.718</td>
</tr>
<tr>
<td>Gross type, n</td>
<td>565/88/124</td>
<td>32/2/3</td>
<td>3.514‡</td>
<td>0.173</td>
</tr>
<tr>
<td>Elevated/flattened/depressed</td>
<td>258/176/343</td>
<td>7/9/21</td>
<td>1.309†</td>
<td>0.566</td>
</tr>
<tr>
<td>Location (long axis), n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper/middle/lower</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology, n</td>
<td>267/34/476</td>
<td>11/3/23</td>
<td>1.030†</td>
<td>0.661</td>
</tr>
<tr>
<td>Invasion depth (M/SM), n</td>
<td>742/35</td>
<td>34/3</td>
<td>1.030†</td>
<td>0.661</td>
</tr>
<tr>
<td>Initial multiplicity, n (%)</td>
<td>51 (6.6)</td>
<td>8 (21.6)</td>
<td>11.912‡</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Z values. †χ² 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.

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. Multivariable 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
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.\(^\text{[30]}\) 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.\(^\text{[31,32]}\) Kato et al.\(^\text{[23]}\) 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.\(^\text{[10]}\) Therefore, we recommend that endoscopic follow-up be longer, such as 10 years, especially for patients with initial multiple neoplasms.

Gastric adenocarcinoma development following \textit{H. pylori} infection progresses from chronic active gastritis, atrophic gastritis, intestinal metaplasia, gastric dysplasia, and finally to gastric adenocarcinoma. Thus, \textit{H. pylori} infection is one of the most important risk factors for gastric cancer.\(^\text{[3]}\) However, it is controversial whether \textit{H. pylori} infection and its eradication affect the incidence of MGN. Some studies have found that \textit{H. pylori} eradication can reduce the incidence of MGN. For example, a study conducted by Nakata et al.\(^\text{[33]}\) using the method of propensity matching showed that successful eradication of \textit{H. pylori} could significantly decrease the incidence of MGN after ESD for EGC; Zhao et al.\(^\text{[34]}\) conducted a meta-analysis and found that successful \textit{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. 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**


