JGH Open An open access journal of gastroenterology and hepatology
Open Access
JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.12989

ORIGINAL ARTICLE

Risk assessment of metachronous gastric cancer after endoscopic submucosal dissection based on endoscopic intestinal metaplasia

Chino Iizuka, Soichiro Sue, Sho Onodera, Aya Ikeda, Ryosuke Ikeda, Yoshihiro Goda, Kuniyasu Irie, Hiroaki Kaneko and Shin Maeda

Department of Gastroenterology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Key words
endoscopic submucosal dissection, intestinal metaplasia, metachronous gastric cancer.

Accepted for publication 16 October 2023.

Correspondence
Shin Maeda, Yokohama City University, Yokohama 236-0004, Japan.
Email: smaeda@yokohama-cu.ac.jp

Declaration of conflict of interest: The authors declare no conflict of interest.
Financial support: This study was supported by Yokohama City University (basic research expenditures).

Funding support: Yokohama City University (basic research expenditures)

Abstract

Background and Aim: The incidence of metachronous gastric cancer (MGC) after endoscopic treatment for early gastric cancer (EGC) is high, but a method of risk assessment for MGC based on endoscopic findings has not been established. In this study, we focused on endoscopic intestinal metaplasia (IM) and investigated the risk for MGC after endoscopic submucosal dissection (ESD) for EGC.
Methods: This retrospective observational study involved patients who underwent curative ESD for EGC from April 2015 to January 2021. We assessed endoscopic IM using the pretreatment endoscopic examination images. The severity of endoscopic IM was classified into four levels: 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Four different gastric areas were evaluated. We divided the patients into a low-score group and a high-score group, and compared the cumulative incidence of MGC.
Results: In total, 156 patients who met the inclusion criteria were followed up for at least 12 months after ESD, and MGC developed in 14 patients during a mean period oof 41.5 months. The endoscopic IM scores in the lesser curvature of the antrum, lesser curvature of the corpus, and greater curvature of the corpus were higher in patients with MGC than in those without MGC. In the corpus, the 5-year cumulative incidence of MGC was significantly higher in the high-score group than in the low-score group (29.8% *vs* 10.0%, $P = 0.004$).
Conclusion: The severity of endoscopic corpus IM was associated with MGC. Thus, patients with severe corpus IM at the time of ESD require careful examination and intensive follow-up.

Introduction

Endoscopic submucosal dissection (ESD) is an effective and minimally invasive treatment for early gastric cancer (EGC).[1,2] However, endoscopic resection spares the gastric mucosa, which increases the risk for metachronous gastric cancer (MGC).[3,4] The cumulative incidence of MGC after endoscopic resection for EGC reportedly ranges from 2.7% to 15.6%.[5]

According to a hypothesis proposed by Correa *et al.*,[6] *Helicobacter pylori* infection causes atrophic gastritis and intestinal metaplasia (IM) followed by dysplasia and eventual gastric cancer. The presence of IM has been reported as a risk factor for primary gastric cancer,[7–9] and patients with severe IM remain at risk for carcinogenesis even after successful *H. pylori* eradication.[10,11]

Histological IM is associated with MGC,[12] but its diagnosis requires biopsy. A real-time and less invasive MGC surveillance method is needed in daily clinical practice. Several classifications of endoscopic IM are available;[13,14] however, studies of endoscopic IM and MGC are scarce, and no method for MGC risk assessment has been established.

In this study, we created a novel endoscopic IM scoring system and evaluated the association between endoscopic IM and the risk of MGC developing after ESD.

Methods

Study design and patients. This was a retrospective observational study. From April 2015 to January 2021, 246 patients underwent ESD for EGC at Yokohama City University Hospital. Patients who underwent curative resection and were followed up for at least 12 months after ESD were eligible. We excluded patients with a history of gastrectomy, with a history of ESD for EGC, without *H. pylori* infection, and with an unknown *H. pylori* infection status. Figure 1 shows the patient recruitment process. This study was approved by the Yokohama

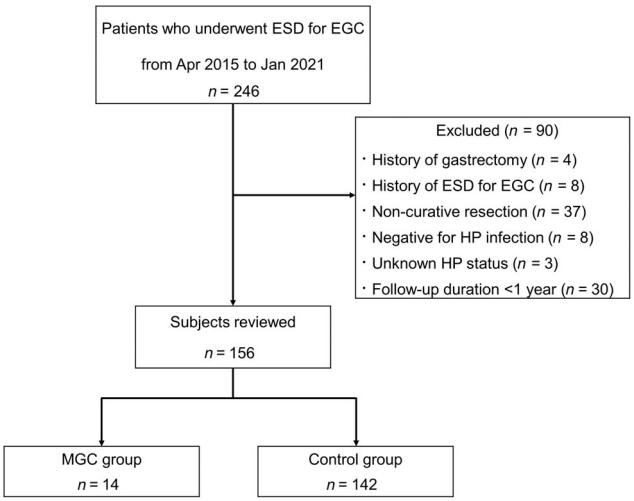

Figure 1 Patient flow diagram. ESD, endoscopic submucosal dissection; EGC, early gastric cancer; HP, *Helicobacter pylori*; MGC, metachronous gastric cancer.

City University Hospital Institutional Review Board (IRB number: F220300004).

Diagnosis of* H. pylori *infection status. To determine the *H. pylori* infection status, we used several techniques including a serum immunoglobulin G (IgG) antibody test, ^{13}C urea breath test, rapid urease test, fecal *H. pylori* antigen test, Giemsa staining, and culture. A positive result for any of these tests was indicative of *H. pylori* infection. If a definite history of eradication therapy was confirmed, the patient was considered to have "past infection" of *H. pylori*. Patients with no eradication history, with negative serum IgG antibody and ^{13}C urea breath tests, and with severe gastric mucosal atrophy were considered to be cases of "spontaneous disappearance." Patients were considered *H. pylori*-negative if serum IgG antibody and ^{13}C urea breath tests were negative without atrophic mucosa.

Clinicopathologic evaluation. The patients' medical records, endoscopic examination and treatment records, and histologic examination results were retrospectively analyzed. We investigated the patients' clinicopathologic characteristics including age, sex, and synchronous occurrence rate, as well as tumor location, size, morphology, histology, depth of invasion, and ulceration. We also examined the presence and severity of atrophy and IM of the background gastric mucosa. We analyzed the occurrence rate of MGC and related factors during the follow-up period.

Endoscopic examination. All patients underwent pretreatment endoscopic examinations to assess the lesion size, location, and morphology. The endoscope used in this study was GIF-H260Z or GIF-H290Z (Olympus Medical Systems Corporation, Tokyo, Japan). We evaluated gastric atrophy using the Kimura–Takemoto classification. Endoscopic IM was evaluated based on the Kyoto classification of gastritis[13] and the scoring system described below.

Scoring system of endoscopic IM. We created an endoscopic scoring system for IM using white-light endoscopy (WLE). Four different areas were evaluated (lesser curvature of the antrum, greater curvature of the antrum, lesser curvature of the corpus, and greater curvature of the corpus). Each area was assigned a score 0 (none), 1 (mild), 2 (moderate), or 3 (severe) according to the severity of IM. The total number of points for all four areas varied from 0 to 12.

The endoscopic diagnostic criteria for IM were as follows: Score 0: flat with no color tone changes in the mucosa; Score 1: rough mucosal surface or villous appearance, or mixed patchy pink and pale areas of mucosa. Map-like redness was also included in this category; Score 2: grayish-white and flat elevated plaques in some but not all areas; Score 3: grayish-white and flat elevated plaques in almost all areas. Representative images of each score are shown in Figure 2.

Two experienced endoscopists (C.I. and S.O.), who were blinded to the patients' background information, examined the

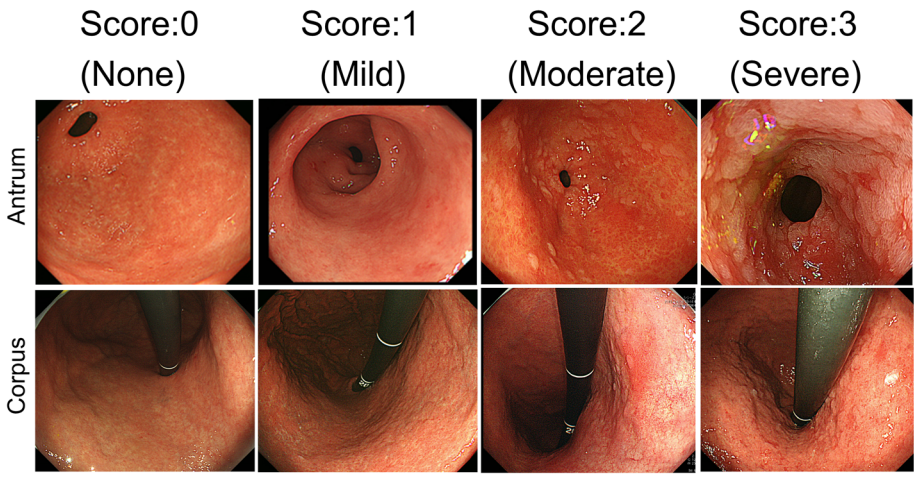

Figure 2 Representative images of endoscopic intestinal metaplasia scores: Score 0 (none), Score 1 (mild), Score 2 (moderate), Score 3 (severe).

images independently and applied the endoscopic IM scoring system. The average value of the two endoscopists' scores was adopted for analysis. When the observers' scores deviated by ≥2 points, a third endoscopist (S.S.) made the final judgment.

ESD and follow-up. The technical methods of ESD have previously been described.[15] The resected specimens were evaluated according to the Gastric Cancer Treatment Guidelines (GCTG) in Japan.[16,17] The resection was considered curative if the specimen had been resected en bloc, had negative tumor margins, and met the criteria for "eCuraA" or "eCuraB" in the GCTG.

The first follow-up endoscopic examination was performed 2 months after the primary ESD to confirm whether the ulceration was healing. Follow-up endoscopy was performed every 12 months thereafter to check for the development of MGC. In these examinations, MGC was defined as gastric cancer detected ≥12 months after ESD, and synchronous lesions were defined as lesions detected <12 months after ESD.

Statistical analysis. Student's *t*-test was used to compare parametric data, and Fisher's exact test was used to analyze nonparametric data including the patients' clinicopathologic characteristics and treatment outcomes. We compared our original endoscopic IM scores between patients with and without MGC by the Mann–Whitney *U* test because the data from the two groups were not normally distributed. The cumulative incidence of MGC was calculated using the Kaplan–Meier method. The log-rank test was used to compare the time-to-event curves of MGC according to the severity of IM.

All *P*-values were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using EZR Version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[18]

Results

Patient characteristics. A total of 246 patients underwent ESD for EGC during the study period. We excluded 4 patients with a history of gastrectomy, 8 patients with a history of ESD for EGC, 37 patients who had undergone noncurative resection, 8 patients diagnosed as negative for *H. pylori* infection, and 3 patients whose *H. pylori* infection status was unknown. In addition, 30 patients were lost to follow-up within 1 year. After excluding these patients, 156 patients were included in our analysis, and 14 patients developed MGC (Fig. 1).

Among the 49 patients who were diagnosed with current *H. pylori* infection at the time of ESD, 47 underwent *H. pylori* eradication therapy after ESD, and eradication was successful in 46 (93.9%) of these patients. The median period from ESD to eradication was 4 months, and 42 patients achieved eradication within 1 year.

The baseline clinicopathologic characteristics of all 156 patients are shown in Table 1. The patients included 125 men and 31 women ranging in age from 42 to 92 years (mean 72.3 ± 7.8 years). The occurrence rate of MGC was 9.6% in men and 6.5% in women, and this difference was not statistically significant. The mean age of the patients in the control group and the MGC group was 72.3 ± 7.9 and 73.1 ± 7.3 years, respectively, with no significant difference. During the follow-up period, 37 additional lesions were detected within 12 months after ESD, and these were considered missed synchronous lesions. With respect to tumor location, 17.9%, 35.3%, and 46.8% of the tumors were in the upper, middle, and lower stomach, respectively. The mean size of the primary lesion was 16.1 ± 11.7 mm. Regarding tumor morphology, 27.6% of the tumors were of the protruded type, 12.8% were of the flat type, and 59.6% were of the depressed type. Histologically, 97.4% and 2.6% of the tumors were differentiated and undifferentiated, respectively. Submucosal invasive carcinoma accounted for 7.7%, and ulceration was confirmed in 3.8%. There were no statistically significant differences in synchronous lesions, location, morphology, size, histology, depth of invasion, or presence of ulceration between the control group and the MGC group.

The background gastric mucosa showed open-type atrophy in 85.3% of patients and closed-type atrophy in 14.7%. According to the Kimura–Takemoto classification of endoscopic atrophy, the occurrence rates of MGC were 0.0% (C1–C2), 3.3% (C3–O1), and 10.9% (O2–O3), and the differences were not statistically significant ($P = 0.448$). With respect to endoscopic IM based on the Kyoto Classification of Gastritis, the MGC occurrence rates were 4.9% (0: none), 4.3% (1: antrum), and 13.9% (2: corpus and antrum), again with no significant difference ($P = 0.158$).

The *H. pylori* infection status at the time of ESD was classified into four groups: "current infection," "eradication in <1 year," "eradication in ≥1 year," and "spontaneous disappearance." The occurrence rate of MGC in each of these four groups was 8.2%, 0.0%, 8.1%, and 18.2%, respectively, with no statistically significant difference ($P = 0.397$).

Analysis of endoscopic IM scores. The endoscopic IM scores according to our novel classification system are shown in Table 2. The MGC group showed higher scores than the control group, and there were statistically significant differences in the lesser curvature of the antrum, lesser curvature of the corpus, and greater curvature of the corpus.

In the gastric corpus, the total scores of the lesser curvature and greater curvature were higher in the MGC group than in the control group (median value, 3.00 *vs* 2.00, respectively; $P = 0.034$), but the total score in the antrum showed no significant difference ($P = 0.059$). The median total score of all four areas was 8.00 in the MGC group and 4.25 in the control group, and the difference was statistically significant ($P = 0.001$).

Analysis of endoscopic IM scores based on H. pylori infection status. We divided the patients into two groups: those with current *H. pylori* infection and those whose *H. pylori* infection had been eradicated <1 year before ESD (Group A, $n = 60$); and those whose *H. pylori* infection had been eradicated ≥1 year before ESD and those with spontaneous disappearance (Group B, $n = 96$). Table 3 shows the endoscopic IM scores of Groups A and B. In Group A, no statistically significant difference was observed between the MGC group and the control group.

Table 1 Baseline characteristics of the 156 patients

Characteristics	Overall ($n = 156$)	MGC group ($n = 14$)	Control group ($n = 142$)	*P*-value
Age (years), mean ± SD	72.3 ± 7.8	73.1 ± 7.3	72.3 ± 7.9	0.710
Sex, *n* (%)				0.738
Male	125 (80.1)	12 (85.7)	113 (79.6)	
Female	31 (19.9)	2 (14.3)	29 (20.4)	
Synchronous multiple EGC, *n* (%)				1.000
Absent	119 (76.3)	11 (78.6)	108 (76.1)	
Present	37 (23.7)	3 (21.4)	34 (23.9)	
Site of the main lesion, *n* (%)				1.000
Upper third	28 (17.9)	2 (14.3)	26 (18.3)	
Middle third	55 (35.3)	5 (35.7)	50 (35.2)	
Lower third	73 (46.8)	7 (50.0)	66 (46.5)	
Size of the main lesion (mm), mean ± SD	16.1 ± 11.7	12.5 ± 6.0	16.4 ± 12.1	0.345
Morphology of the main lesion, *n* (%)				1.000
Elevated	43 (27.6)	4 (28.6)	39 (27.5)	
Flat	20 (12.8)	2 (14.3)	18 (12.7)	
Depressed	93 (59.6)	8 (57.1)	85 (59.9)	
Histology, *n* (%)				0.316
Differentiated type	152 (97.4)	13 (92.9)	139 (97.9)	
Undifferentiated type	4 (2.6)	1 (7.1)	3 (2.1)	
Depth of invasion, *n* (%)				0.603
Mucosa	144 (92.3)	14 (100)	130 (91.5)	
Submucosa	12 (7.7)	0 (0.0)	12 (8.5)	
Ulcer or scar, *n* (%)				0.437
Negative	150 (96.2)	13 (92.9)	137 (96.5)	
Positive	6 (3.8)	1 (7.1)	5 (3.5)	
Atrophic gastritis[†], *n* (%)				0.448
C1–C2	7 (4.5)	0 (0.0)	7 (4.9)	
C3–O1	30 (19.2)	1 (7.1)	29 (20.4)	
O2–O3	119 (76.3)	13 (92.9)	106 (74.6)	
Intestinal metaplasia[‡], *n* (%)				0.158
0 (None)	61 (39.1)	3 (21.4)	58 (40.8)	
1 (Antrum)	23 (14.7)	1 (7.1)	22 (15.5)	
2 (Corps and antrum)	72 (46.2)	10 (71.4)	62 (43.7)	
H.pylori infection status, *n* (%)				0.397
Current infection	49 (31.4)	4 (28.6)	45 (31.7)	
Eradication in <1 year	11 (7.1)	0 (0.0)	11 (7.7)	
Eradication in ≥1 year	74 (47.4)	6 (42.9)	68 (47.9)	
Spontaneous disappearance	22 (14.1)	4 (28.6)	18 (12.7)	

MGC, metachronous gastric cancer; SD, standard deviation; EGC, early gastric cancer; ESD, endoscopic submucosal dissection.
[†]Kimura-Takemoto classification.
[‡]Kyoto classification of gastritis.

In Group B, the MGC group showed a significant difference in the greater and lesser curvatures of the corpus, and the median total score of the corpus was 3.50 in the MGC group and 2.00 in the control group ($P = 0.003$). In Group B, the median total score of all four areas was 7.75 in the MGC group and 4.25 in the control group, with a statistically significant difference ($P = 0.002$).

Cumulative incidence of MGC. All 156 patients were followed up for a median duration of 41.5 months (range, 12–86 months). In total, 14 patients developed MGC during the follow-up period. The median period from ESD to detection of MGC was 26 months (range, 13–50 months). All cases of MGC were detected as EGC. The annual incidence rate of MGC per 1000 person-years was 2.5%, and the cumulative 3- and 5-year incidence of MGC after ESD was 7.3% and 13.3%, respectively.

Kaplan–Meier analysis. We divided the patients into a low-score group (0–3 points) and a high-score group (4–6) using the total IM scores of the greater and lesser curvatures.

In the antrum, the 3-year cumulative incidence of MGC in the low- and high-score groups was 5.2% and 12.9%, respectively, and the 5-year cumulative incidence was 9.7% and 22.3%, respectively. The cumulative incidence of MGC showed

Table 2 Median value of endoscopic intestinal metaplasia (IM) scores

	MGC group ($n = 14$)	Control group ($n = 142$)	*P*-value
Antrum			
a) Lesser curvature	1.75	1.00	0.048
b) Greater curvature	1.50	1.25	0.123
Total (a + b)	3.50	2.50	0.059
Corpus			
c) Lesser curvature	2.50	2.00	0.011
d) Greater curvature	1.00	0.50	0.0095
Total (c + d)	3.00	2.00	0.004
Antrum + corpus (a + b + c + d)	8.00	4.25	0.001

MGC, metachronous gastric cancer.

Table 3 Median value of endoscopic intestinal metaplasia (IM) scores in groups A and B

	Group A ($n = 60$)			Group B ($n = 96$)		
	MGC ($n = 4$)	Control ($n = 56$)	*P*-value	MGC ($n = 10$)	Control ($n = 86$)	*P*-value
Antrum						
a) Lesser curvature	2.75	1.50	0.185	1.50	1.00	0.069
b) Greater curvature	2.75	1.50	0.358	1.50	1.00	0.155
Total (a + b)	5.00	2.50	0.245	3.00	2.50	0.081
Corpus						
c) Lesser curvature	1.75	1.50	0.432	2.00	1.50	0.017
d) Greater curvature	0.50	0.50	0.988	1.00	0.50	0.003
Total (c + d)	2.50	2.00	0.520	3.50	2.00	0.003
Antrum + corpus (a + b + c + d)	8.00	4.25	0.190	7.75	4.25	0.002

MGC, metachronous gastric cancer; Group A, patients with current *H. pylori* infection and patients whose *H. pylori* infection had been eradicated <1 year before ESD; Group B, patients whose *H. pylori* infection had been eradicated ≥1 year before ESD and patients with spontaneous disappearance.

no significant difference according to the severity of antrum IM ($P = 0.068$ by log-rank test) (Fig. 3a).

In the corpus, the 3-year cumulative incidence of MGC in the low- and high-score groups was 4.5% and 22.7%, respectively, and the 5-year cumulative incidence was 10.0% and 29.8%, respectively. There was a statistically significant difference in the cumulative incidence of MGC according to the severity of corpus IM ($P = 0.004$ by log-rank test) (Fig. 3b).

Discussion

In this retrospective study, we assessed the MGC risk using a novel endoscopic IM scoring system. We found that the severity of endoscopic corpus IM was associated with the incidence of MGC that developed after ESD.

IM is an important risk factor for MGC.[19,20] Several studies have shown that histologic corpus IM is a risk factor for MGC.[21–23] A recent meta-analysis reported an odds ratio of 3.15 (95% confidence interval, 1.67–5.96).[12] However, histologic examination allows the evaluation of only the biopsy point; it is not possible to evaluate a wide area of the stomach. Endoscopic assessment can overcome this limitation. A few endoscopic studies have investigated the association between IM and MGC, and two retrospective studies have shown that endoscopic IM is a risk factor for MGC.[24,25] However, a detailed classification of IM was not performed in these studies; the authors only investigated whether IM was present or absent.

In the current study, the corpus IM score was higher in the MGC group than in the control group (Table 2), and the 3- and 5-year cumulative incidence of MGC was higher in patients with severe corpus IM (Fig. 3b). This is the first study to show that the endoscopic corpus IM score was higher in patients with MGC than without MGC, and this result is consistent with previous reports showing similar results histologically.[21–23] Histologic assessment of IM according to the updated Sydney system of gastritis is the gold standard, but diagnosis is time consuming and expensive, and biopsies are invasive to patients. If endoscopic IM evaluation becomes useful, it will be more efficient to assess the MGC risk. In this study, the number of patients with MGC was small ($n = 14$) but a statistically significant difference was found. Thus, our IM scoring system may have high power for predicting MGC.

Several studies have revealed a relationship between primary gastric cancer and the Kyoto classification of gastritis.[26–29] However, few studies have investigated the association between MGC and the Kyoto classification. One retrospective study

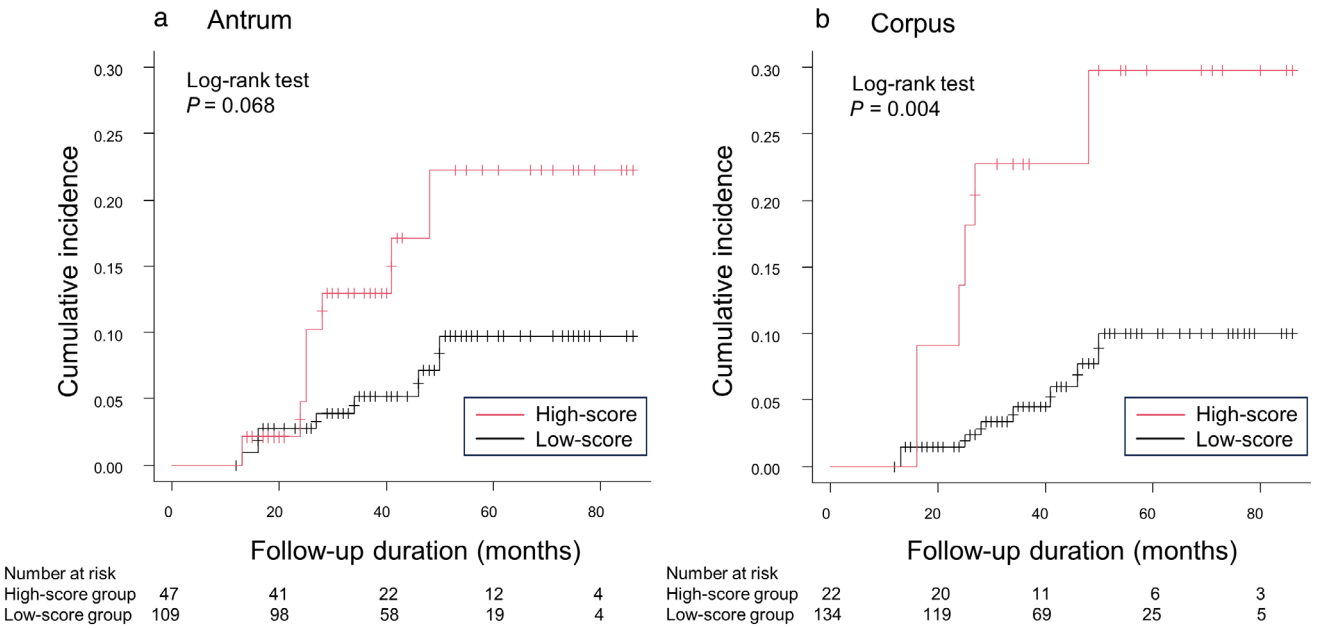

Figure 3 Kaplan–Meier estimates of the cumulative incidence of metachronous gastric cancer (MGC) according to the severity of intestinal metaplasia (IM) in the antrum (a) and corpus (b).

compared the IM score according to the Kyoto classification between patients with de novo cancer and patients with MGC, and no significant differences were found.[28] In the present study, the classification of IM based on the Kyoto classification showed no statistically significant difference in the incidence rate of MGC, consistent with the aforementioned study (Table 1). In our novel IM scoring system, however, the MGC group showed higher IM scores in the gastric corpus, and a statistically significant difference was observed (Table 2). Our IM scoring system evaluates four gastric areas and provides a score of 0, 1, 2, or 3 points for each area; thus, it is considered to facilitate a more detailed evaluation than the Kyoto classification.

Because the sensitivity of narrow-band imaging (NBI) to IM is higher than that of WLE (87% *vs* 53%; $P < 0.001$), an endoscopic grading of gastric IM (EGGIM) system using NBI was recently proposed and demonstrated to be useful.[14] EGGIM is well associated with the Operative Link on Gastritis/IM Assessment (OLGIM), the histologic staging system of gastric IM.[30–32] However, whether EGGIM is useful for risk assessment of MGC remains unclear.[12] EGGIM provides a score of 0, 1, or 2 in five areas, and 30% of the IM-affected area is the boundary between a score of 1 and a score of 2; this requires some skill for accurate judgment. In addition, imaging the entire background gastric mucosa with NBI after WLE observation lengthens the time of endoscopic examination. In our IM scoring system, the evaluation of IM by WLE depends on the method proposed by the Kyoto Classification of Gastritis, and we focus on the presence and extent of the grayish-white and flat elevated plaques.[13,26] The grayish-white and flat elevated plaques are the features that can be most easily detected by WLE; their detection does not require a high skill level, and the examination time is not extended.

Several studies have shown that the severity of corpus IM is a risk factor for MGC regardless of the *H. pylori* status.[21,22] In this study, patients who achieved eradication ≥1 year before ESD and patients with spontaneous disappearance (Group B) showed higher corpus IM scores in the MGC group than in the control group; however, there were no significant differences in patients with current infection at the time of ESD and patients who achieved eradication <1 year before ESD (Group A) (Table 3). The presence of severe corpus IM despite the fact that *H. pylori* was eradicated long ago may represent a "point of no return" at which the development of gastric cancer is difficult to prevent.

We recognize that this study had some limitations. First, it was a single-center, retrospective study. Second, we performed only a univariate analysis of the risk factors for MGC. We judged that it was not statistically appropriate to introduce a multivariate analysis because of the small number of patients. It will be necessary to enroll more patients and conduct a multicenter study in the future.

Conclusion

In summary, we found that the severity of endoscopic corpus IM was associated with MGC. Thus, patients with severe corpus IM at the time of ESD should be carefully examined and undergo intensive follow-up.

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