学位論文

Endoscopic causes and characteristics of missed gastric cancers after endoscopic submucosal dissection

初回内視鏡治療後に発見された見逃し胃癌の原因と特徴

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ABSTRACT

Background and Aims

As endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) preserves the entire stomach, missed gastric cancers (MGCs) are often found in the remaining gastric mucosa. However, the endoscopic causes of MGCs remains unclear. Therefore, I aimed to elucidate the endoscopic causes and characteristics of MGCs after ESD.

Methods

From 01/2009–12/2018, all patients with ESD for initially detected EGC were enrolled. According to a review of esophagogastroduodenoscopy (EGD) images before ESD, we identified the endoscopic causes (perceptual, exposure, sampling errors, and inadequate preparation) and characteristics of MGC in each endoscopic cause.

Results

In total, 2208 patients who underwent ESD for initial EGC were analyzed. Of these, 82 (3.7%) patients had 100 MGCs. The breakdown of the endoscopic causes of MGCs was as follows: 69 (69%) perceptual errors, 23 (23%) exposure errors, 7 (7%) sampling errors, and 1 (1%) inadequate preparation. Logistic regression analysis showed that the risk factors for perceptual error were male sex (Odds ratio [OR], 2.45; 95% Confidence interval [CI], 1.16-5.18), isochromatic coloration (OR, 3.17; 95% CI, 1.47–6.84), greater curvature (OR, 2.31; 95% CI, 1.121–4.40), and lesion size ≤12 mm (OR, 1.74; 95% CI,

1.07–2.84). The sites of exposure errors were around incisura angularis, 11 (48%); posterior wall of the gastric body, 6 (26%); and antrum, 5 (21%).

Conclusions

I identified MGCs in four categories and clarified their characteristics. Quality improvements in EGD observation, with attention to the risks of perceptual and site of exposure errors, can potentially prevent missing EGCs.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is an accepted treatment for early gastric cancer (EGC) without lymph node metastasis.[1,2] Several studies have demonstrated a good prognosis in patients who undergo ESD for EGC.[3, 4] However, due to the preservation of the entire stomach after ESD, premalignant mucosae have a high risk of giving rise to metachronous gastric cancers.[5, 6] Metachronous gastric cancer detected early after ESD is considered a missed cancer and is a concern in clinical practice. The rate of missed gastric cancer (MGC) ranges from 0.87% to 19.2%,[6-16] of which the rate of missed invasive gastric cancer ranges from 0.4% to 0.8% in Japan and Korea.[12, 15, 16] Reducing the number of missed lesions is important because such lesions may require a patient to undergo surgery. However, studies on missed cancer have focused on its incidence, and information on the endoscopic cause of MGC is limited. Identifying the endoscopic cause can contribute to the improvement of endoscopic examination quality. Therefore, I aimed to identify the endoscopic causes of MGC and the characteristics associated with each endoscopic cause.[34]

METHODS

Study population

In this retrospective study, patients who underwent ESD for initial EGC at Shizuoka Cancer Center from January 2009 to December 2018 were eligible for inclusion. The following patients were excluded: those who underwent additional gastrectomy after ESD and those who did not undergo surveillance esophagogastroduodenoscopy (EGD) at Shizuoka Cancer Center. Written informed consent for examination and treatment was obtained from all patients before the procedure. This study was approved by the Institutional Review Board of Shizuoka Cancer Center (institutional study number: J2022-72-2022-1-3).

Endoscopic examination

To minimize the time and effort required to remove mucus and bubbles from the mucosal surface during the examination, patients were asked to drink water mixed with mucolytic and defoaming agents before the procedure. The formula of the preparation for EGD in our institution was 100 mL of water containing 20,000 units of pronase (Kaken Pharmaceutical, Tokyo, Japan), 80 mg of simethicone (Horii Pharmaceutical Ind., Osaka Japan), and 1 g of sodium bicarbonate. Endoscopic examination was performed using a

video endoscope (GIF-H260Z and GIF-H290Z; Olympus Medical, Tokyo, Japan) with midazolam and pethidine hydrochloride for sedation and pain reduction, unless there was a contraindication or patient refusal. If any food residue or mucus remained in the stomach during endoscopy, it was removed as much as possible to ensure clear observation of the mucosal surface. To map the entire stomach, I performed a procedure modified from already published screening protocol,[17 -19] the procedure series was composed 35 endoscopic images. First, I took endoscopic images of the pylorus and the four quadrants (lesser curvature, anterior wall, greater curvature, and posterior wall) of the antrum, lower gastric body, middle gastric body, and upper gastric body in the forward view. After the forward view, I took three endoscopic images (anterior wall, greater curvature, and posterior wall) from the fornix while the endoscope was inverted at the fornix. Then, I took endoscopic images of the three quadrants (lesser curvature, anterior wall, and posterior wall) of the cardia, upper gastric body, middle gastric body, lower gastric body, and incisura angularis in the retroflexion view. In summary, a total of 35 images were taken, 17 in the forward view and 18 in the retroflexion view. When a lesion was suspected to be gastric cancer, it was confirmed as cancer by biopsy.

Surveillance protocol after ESD

Surveillance EGDs were performed 2–3 months after ESD to mainly confirm ulcer healing, and annually thereafter. This was based on our institutional protocol, which was a modification of the ESD guidelines for EGC.[1, 2]

Definitions

I defined MGC as gastric cancer that was diagnosed within 18 months after the initial ESD according to our institutional EGD surveillance protocol. I excluded cases of local recurrence.

The endoscopic causes of MGC were classified into the following four categories:

(1) Perceptual error: the lesion was not diagnosed on EGD before ESD, but could be recognized retrospectively on endoscopic images (Fig. 1).

(2) Exposure error: the lesion was neither diagnosed nor captured during EGD before ESD (Fig. 2).

(3) Inadequate preparation: adequate observation could not be performed because of the large amount of food residue or mucus that could not be removed (Fig. 3).

(4) Sampling error: the cancer was biopsied by EGD before ESD but diagnosed as a noncancerous lesion (Fig. 4).

Two endoscopists (Y. Yabuuchi and Y. Yamamoto, board-certified fellows of the Japan Gastroenterological Endoscopy Society), who were blinded to the clinicopathological information, independently reviewed the endoscopic images taken according to the observation protocol during EGD before ESD and classified the endoscopic cause of the MGC. If the diagnoses were not identical, a consensus was reached after reviewing the endoscopic images again.

Tumor location was classified according to the Japanese Classification of Gastric Carcinoma.[20] For a more detailed evaluation of the site of perceptual error, the stomach was divided into the fornix, cardia, upper gastric body, middle gastric body, lower gastric body, incisura angularis, and antrum. I identified the area 2 cm away from the incisura angularis, which was defined as the bending region along the lesser curvature between the gastric body and antrum, i.e., "area around the incisura angularis." The endoscopic characteristics of the cancers were classified according to the Paris endoscopic classification.[21] To assess the main macroscopic type in relation to the detection of MGC, the macroscopic type was classified based on the pathognomonic macroscopic type according to the Paris classification: protruded all types, 0-I, 0-I+0-IIa, and 0-I+0-IIc; excavated type, 0-IIc+III; elevated type, 0-IIa and 0-IIa+0-IIb; flat/depressed type, 0-Iib, 0-IIc, or a combination of these two types; and mixed type, a combination of elevated and

depressed types. *Helicobacter pylori* status was evaluated based on the patients' medical records and interview. Colorations were classified as pale, reddish, or isochromatic, based on endoscopy reports. I classified the curability of endoscopic resections into endoscopic curability (eCura) A, B, C-1, and C-2, according to the Japanese Gastric Cancer Association guidelines version 5. Compared with past guidelines, eCuraA and eCuraB corresponded to curative resection, while eCuraC corresponded to noncurative resection. Among eCuraC cases, those with histological factors satisfying curative resection but with piecemeal resection or positive horizontal margin were subclassified as eCuraC-1, whereas all other noncurative resections were subclassified as eCuraC-2. Experts were defined as endoscopists who performed >1000 EGDs per year on average during the study period and those who performed EGD or ESD procedures independently. Trainees were defined as endoscopists who performed EGD or ESD under the supervision of experts.

Study endpoints

This study aimed to (1) estimate the proportion of MGCs; (2) classify the endoscopic cause of MGCs; (3) identify the characteristics of MGCs in each endoscopic cause; and (4) identify the characteristics of MGCs required to undergo surgery.

Statistical analyses

Categorical variables are presented as counts and percentages, and continuous variables are summarized as medians and interquartile ranges. Statistical analyses were performed using Student's t-test or Fisher's exact test for univariate analysis. The lesion size cut-off for perceptual error was determined using the Youden index, which is defined as the maximum vertical distance between the receiver operating characteristic curve and the diagonal line. The characteristics of perceptual error with $p < 0.10$ on univariate logistic regression analysis using sex, age, *Helicobacter pylori* status, site, macroscopic type, coloration, size, and endoscopist were entered into a multivariate logistic regression analysis, and the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using EZR (version 1.40; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[22]

RESULTS

I identified 3112 patients who underwent ESD for initially detected EGC from January 2009 to December 2018. After reviewing the additional surgery and surveillance EGD data, 904 patients were excluded. Thus, 2208 patients with 2584 lesions were included in the analysis. In this population, 83 patients were diagnosed with gastric cancer within 18 months after the initial ESD. After one patient was excluded with a diagnosis of recurrence, 82 patients with 100 lesions were diagnosed with MGC, accounting for 3.7% of all analyzed patients with EGC (Fig. 5). The clinicopathological characteristics of the MGCs and initially detected EGC are summarized in Table 1. The median size of the MGC group was 12.5 mm (interquartile range: 8–18), and significantly smaller than that of the initially detected EGCs group.

Incidence and endoscopic causes of the MGCs

Of the 100 lesions of MGCs, 69 (69%), 23 (23%), 7 (7%), and 1 (1%) were attributed to perceptual error, exposure error, sampling error, and inadequate preparation, respectively (Fig. 6).

Risk factors for perceptual error

Of the 100 lesions of MGCs, 69 (69%) were attributed to perceptual error. Lesion size ≤ 12 mm was the variable in the analysis based on the Youden index. There was an association between male sex and perceptual error (OR, 2.45; 95% CI, 1.16–5.18) compared with the initial ESD group (Table 2). The lesion on the greater curvature was significantly associated with increased perceptual errors (OR, 2.31; 95% CI, 1.121–4.40), lesion size ≤ 12 mm (OR, 1.74; 95% CI, 1.07–2.84), and isochromatic coloration (OR, 3.17; 95% CI, 1.47–6.84). There was no difference between the group that performed by 20 trainees and performed by 7 experts in terms of perceptual error.

Characteristics of exposure error

Of the 100 lesions of MGCs, 23 (23%) were attributed to exposure error. In one patient, endoscopic examination was not correctly performed according to our modified screening protocol during EGD, which a trainee performed. The remaining 22 lesions were classified into three groups: the posterior wall of the gastric body, area around the incisura angularis, and antrum. The sites of exposure error were as follows: 11 (48%), area around the incisura angularis; 6 (26%), posterior wall of the gastric body; and 5 (21%), antrum (Table 3). In lesions with exposure error found on the posterior wall of the gastric body,

all endoscopic examinations before ESD were performed by trainees. Around incisura angularis, trainees missed 6 (54%) cases. On antrum, trainees missed 2 (40%) cases.

Characteristics of MGCs required to undergo surgery

Five (5%) of all MGCs required surgery due to the high risk of harboring lymph node metastasis. Four lesions were attributable to perceptual errors and one to inadequate preparation (Supplementary Table 1). An endoscopic image of an MGC requiring surgery is presented in Fig. 3 and Supplementary Fig. 1-4.

DISCUSSION

Herein I investigated the endoscopic causes of MGCs after ESD for initial EGC. In this large-scale study, 69% and 23% of MGCs were attributable to perceptual and exposure errors, respectively. Furthermore, I found that the greater curvature, isochromatic coloration, and smaller size were risk factors for perceptual errors, whereas the posterior wall of the gastric body, area around the incisura angularis, and antrum were risk factors for exposure errors. By paying attention to these findings in daily examinations, missed cancers may be prevented or detected at an earlier stage.

It has been reported that systematic observation protocols, such as the systematic alphanumeric coded endoscopy, have contributed to improving gastric cancer detection.[23,24] However, although this method can help ensure the examination quality, it cannot completely eliminate missed lesions. Therefore, it is important to understand the most frequently occurring endoscopic errors. Herein I classified the endoscopic cause of MGCs and identified the characteristics of MGCs in each endoscopic cause. Several studies have reported on MGCs; however, few studies have categorized the endoscopic cause of MGC by retrospectively examining the associated endoscopic images. The strength of our study was that I were able to determine how cancers were missed and how this could have been counteracted, by determining the characteristics of these errors.

Perceptual error was the most frequent type of error in this study. I found that a lesion size ≤ 12 mm, lesions on the gastric curvature, isochromatic coloration, and male sex were risk factors for perceptual errors. Previous studies reported that MGCs tended to be smaller,[9, 10] and that all missed gastric neoplasms were ≤ 10 mm.[12] However, there has been no information on the coloration or location of cancers that are difficult to recognize; these characteristics are clarified in this study. I hypothesized that the area of the greater curvature tended to be observed at a distance during screening endoscopic examination of the stomach, and that cancers of isochromatic coloration were camouflaged by the surrounding gastric mucosa. Considering sex, it has been reported that men are more likely to have synchronous EGC.[25] This means that even if EGC is found during endoscopic examination there is a high probability that other lesions are present, thus leading to missed cancer. Exposure error was the second-most frequent type of error, and was found to be associated with the following three locations: posterior wall of the gastric body, area around the incisura angularis, and antrum. The posterior wall of the gastric body and incisura angularis were reported to be blind spots during endoscopic screening examination.[12,26] In addition, the antrum was identified as an area that was not adequately observed in this study. Although the antrum seemed to be an easy area to observe, peristalsis and indentation may cause blind spots (Supplementary Fig. 5). Interestingly,

exposure errors around the incisura angularis area and the antrum occurred regardless of the experience of endoscopists, whereas those in the posterior wall of the gastric body occurred only with trainees. This result suggested that exposure errors around the incisura angularis area and the antrum could occur as human errors for any endoscopist, while blind spots in the posterior wall of the body were more likely to occur for novice endoscopists. Additionally, this result suggested that blind spots can exist even when endoscopic observation is performed according to the protocol.

As long as endoscopic examination is performed by humans, human error is inevitable. The risk of perceptual errors may increase with fatigue and loss of concentration. A prior study reported that 75% of metachronous cancers were missed cancer.[27] In recent years, there have been reports of artificial intelligence for detecting EGC.[28-30] In the future, perceptual errors may be reduced using these artificial intelligence systems. Regarding exposure error, there is a technical aspect of whether or not the area can be delineated. Even if you have decided how to observe the entire stomach, there are areas that are prone to blind spots. Unless the area where cancer exists is examined, the lesion cannot be detected even with the support of artificial intelligence. Recently, there has been a report of a real-time quality improvement system based on a deep convolutional neural network that supports how the stomach is completely observed.[26] This system can solve the

problem of blind spots.

This study has some limitations that should be acknowledged. First, the analysis was performed at a single tertiary hospital. Second, only still images were reviewed for etiological classification of missed cancers. Thus, because videos were not reviewed, additional information other than that present in the images taken was lacking. Third, I defined MGCs as lesions diagnosed within 18 months after the initial ESD according to our institutional EGD surveillance protocol; however, cancers found within 12 months after the initial examination are generally considered missed cancers.[9-11] However, given the relatively long natural course of EGC[31-33] and the fact that the incidence of missed cancers in this study was consistent with previous data,[6-11, 13-16] varying the period of defining MGCs would have little effect. Fourth, the *Helicobacter pylori* status, which could have an effect on MGCs, was unknown in nearly half of this study's patient population.

In summary, MGCs were detected in 3.7% of patients who underwent ESD for initial EGC, most of which could be explained by perceptual and exposure errors. Quality improvements in the performance of EGD, with attention paid to the risk of perceptual error and the exposure error-prone sites, have the potential to prevent missed cancer.

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FIGURE LEGENDS

Figure 1. Representative images of perceptual error.

Left) Initial EGD. A reddish and slightly elevated lesion was recognized on the greater curvature of the antrum (white arrowhead).

Right) Surveillance EGD. The same lesion was recognized (white arrowhead). This lesion was classified as perceptual error.

EGD, esophagogastroduodenoscopy

Figure 2. Representative images of exposure error.

Left) Initial EGD. Initial early gastric cancer was recognized on the lesser curvature of the antrum (white arrowhead). Missed cancer was not captured in the initial EGD images.

Right) Surveillance EGD. An ulcer scar after endoscopic submucosal dissection was recognized on the lesser curvature of the antrum (white arrowhead). An isochromatic and slightly elevated lesion was recognized on the anterior wall of the antrum around the incisura angularis (green arrowhead). This lesion was classified as an exposure error.

EGD, esophagogastroduodenoscopy

Figure 3. Representative images of inadequate preparation.

Left) Initial EGD. Initial early gastric cancer was recognized on the anterior wall of the antrum (white arrowhead).

Middle) Initial EGD. A large amount of food residue or mucus remained and could not be removed. The gastric body was not easily visible.

Right) Surveillance EGD. An ulcer scar after endoscopic submucosal dissection was recognized on the anterior wall of the antrum (white arrowhead). An isochromatic and slightly elevated lesion with depression was recognized on the posterior wall of the lower gastric body (green arrowhead). This lesion was classified as an inadequate preparation.

EGD, esophagogastroduodenoscopy

Figure 4. Representative images of sampling error.

Left) Initial EGD. A reddish and elevated lesion was recognized on the lesser curvature of the antrum (white arrowhead). The result of the biopsy was non-neoplastic in this EGD.

Right) Surveillance EGD. The same lesion was recognized (white arrowhead). The result of the biopsy was neoplastic in this EGD. This lesion was classified as a sampling error.

EGD, esophagogastroduodenoscopy

Figure 5. Patient flowchart.

ESD, endoscopic submucosal dissection; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; GC, gastric cancer; MGC, missed gastric cancer

Figure 6. The algorithm to classify the endoscopic cause of missed cancer.

MGC, missed gastric cancer; EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection

TABLES

Table 1. Clinicopathological characteristics of MGCs and initially detected EGCs.

	MGCs 82 patients/100 lesions	Initially detected EGCs 2208 patients/2584 lesions	P value
Patients			
Age, years, median (IQR)	73 (68–78)	72 (66–78)	0.399
Sex, n (%)			0.051
Male	69 (84.1)	1648 (74.6)	
Female	13 (15.9)	560 (25.4)	
H. pylori status, n (%)			0.187
Eradicated	21 (25.6)	371 (16.8)	
Infected	20 (24.4)	584 (26.5)	
Naïve	1 (1.2)	23 (1.0)	
Unknown	40 (48.8)	1230 (55.7)	
Lesions			
Size, mm, median (IQR)	12.5 (8–18)	16 (10–25)	< 0.001
Histological type, n (%)			0.229
Differentiated	93 (93.0)	2466 (95.4)	
Undifferentiated	7 (7.0)	118 (4.6)	
Depth, n (%)			0.779
T1a (M)	93 (93.0)	2322 (89.9)	
T1b1 (SM1)	5 (5.0)	168 (6.5)	
T1b2 (SM2)	2 (2.0)	90 (3.5)	
T2 (MP) or deeper	0	4 (0.1)	
Ulcerative findings, n (%)			0.701
Negative	94 (94.0)	2385 (92.3)	
Positive	6 (6.0)	199 (7.7)	
Treatment, n (%)			< 0.001
ESD only	95 (95.0)	2584 (100)	
Surgery	2 (2.0)	0 (0)	
ESD and additional surgery	3 (3.0)	0 (0)	
eCura, n (%)			0.105
A	90 (91.8)	2236 (86.5)	
B	5 (5.1)	95 (3.7)	
C-1	0 (0)	8 (0.3)	
C-2	3 (3.1)	245 (9.5)	

MGC, missed gastric cancer; EGC, early gastric cancer; IQR, interquartile range; *H. pylori*, *Helicobacter pylori*; M, mucosa; SM1, superficial submucosa (tumor invasion is less than 500 μm from the muscularis mucosae); SM2, deep submucosa (tumor invasion is 500 μm or deeper from the muscularis mucosae); MP, muscularis propria; eCura, endoscopic curability; ESD, endoscopic submucosal dissection

Table 2. Logistic regression analysis of risk factors associated with perceptual error.

		All lesions*, n	Perceptual error lesions, n (%)	Univariate analysis		Multivariate analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Sex	Female	641	8 (1)	1 (Ref)			
	Male	2012	61 (3)	2.47 (1.18–5.20)	0.019	2.45 (1.16–5.18)	0.018
Age, years	≤ 72	1308	34 (3)	1 (Ref)			
	> 72	1345	35 (3)	1.00 (0.62–1.62)	0.996		
H. pylori status	Eradicated	425	8 (3)	1 (Ref)			
	Infected	728	19 (2)	1.40 (0.61–3.22)	0.43		
	Naïve	24	0	Not evaluated			
	Unknown	1476	42 (3)	1.53 (0.71–3.28)	0.28		
Site 1	Upper third	456	13 (3)	1.28 (0.65–2.53)	0.474		
	Middle third	1080	31 (3)	1.29 (0.76–2.20)	0.348		
	Lower third	1117	25 (2)	1 (Ref)			
Site 2	Lesser curvature	1173	21 (2)	1 (Ref)			
	Anterior wall	468	15 (3)	1.82 (0.93–3.55)	0.081	1.75 (0.88–3.43)	0.106
	Greater curvature	458	18 (4)	2.24 (1.18–4.25)	0.013	2.31 (1.21–4.40)	0.011
	Posterior wall	554	15 (3)	1.54 (0.78–2.98)	0.216	1.51 (0.77–2.91)	0.233
Macroscopic type	Elevated	764	21 (3)	1 (Ref)			
	Flat/depressed	1530	47 (3)	1.12 (0.67–1.89)	0.665	1.02 (0.60–1.74)	0.944
	Excavated	8	0	Not evaluated			
	Protruded	143	0	Not evaluated			
	Mixed	208	1 (0)	0.17 (0.02–1.27)	0.084	0.16 (0.02–1.21)	0.076
Coloration	Pale	663	9 (1)	1 (Ref)			
	Reddish	644	33 (2)	1.83 (0.87–3.84)	0.118	1.74 (0.82–3.72)	0.150
	Isochromatic	1346	27 (4)	3.18 (1.48–6.82)	0.002	3.17 (1.47–6.84)	0.003
Size	> 12 mm	1650	31 (2)	1 (Ref)		1 (Ref)	
	≤ 12 mm	1003	38 (4)	2.06 (1.27–3.33)	0.003	1.74 (1.07–2.84)	0.026

Endoscopist	Expert	1433	37 (3)	1 (Ref)	
	Trainee	1220	32 (3)	1.02 (0.63–1.64)	0.947

*All lesions (n=2653) were the sum of perceptual error lesions (n=69) and initially detected EGC lesions (n=2584).

EGC, early gastric cancer; OR, odds ratio; CI, confidence interval; *H. pylori*, *Helicobacter pylori*

Table 3. Characteristics of exposure error.

Lesion number	Site 1	Site 2	Endoscopist	Classification
1	U	PW	Trainee	Body, posterior wall
2	U	PW	Trainee	Body, posterior wall
3	U	PW	Trainee	Body, posterior wall
4	M	PW	Trainee	Body, posterior wall
5	M	PW	Trainee	Body, posterior wall
6	M	PW	Trainee	Body, posterior wall
7	M	LC	Trainee	Around incisura angularis
8	M	LC	Expert	Around incisura angularis
9	M	AW	Expert	Around incisura angularis
10	M	AW	Trainee	Around incisura angularis
11	M	AW	Trainee	Around incisura angularis
12	M	PW	Expert	Around incisura angularis
13	M	PW	Trainee	Around incisura angularis
14	L	LC	Expert	Around incisura angularis
15	L	LC	Trainee	Around incisura angularis
16	L	AW	Trainee	Around incisura angularis
17	L	PW	Expert	Around incisura angularis
18	L	LC	Trainee	Antrum
19	L	LC	Trainee	Antrum
20	L	GC	Expert	Antrum
21	L	PW	Expert	Antrum
22	L	PW	Expert	Antrum
23	M	LC	Trainee	Not follow the screening protocol

U, upper third; M, middle third; L, lower third; PW, posterior wall; LC, lesser curvature; AW, anterior wall; GC, greater curvature

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1.

Left) Initial EGD. An isochromatic and flat lesion with rough membrane was recognized on the greater curvature of the lower gastric body (white arrowhead).

Right) Surveillance EGD. A slightly reddish and flat lesion was recognized on the same location (white arrowhead). The lesion was classified as a perceptual error.

EGD, esophagogastroduodenoscopy

Supplementary Figure 2.

Left) Initial EGD. An isochromatic and slightly depressed lesion was observed on the anterior wall of the middle gastric body (white arrowhead).

Right) Surveillance EGD. The same lesion was recognized (white arrowhead). The lesion was classified as a perceptual error.

EGD, esophagogastroduodenoscopy

Supplementary Figure 3.

Left) Initial EGD. Initial early gastric cancer was recognized on the lesser curvature of the middle gastric body (white arrowhead). An uneven mucosal area with slight blood adherence was recognized on the incisura angularis area (green arrowhead).

Right) Surveillance EGD. An ulcer scar after endoscopic submucosal dissection was recognized on the lesser curvature of the middle gastric body (white arrowhead). An isochromatic and slightly depressed lesion with slight blood adherence was recognized on the incisura angularis (green arrowhead). The lesion was classified as a perceptual error.

EGD, esophagogastroduodenoscopy

Supplementary Figure 4.

Left) Initial EGD. A lesion with combination of slight elevation and depression was recognized on the anterior wall of the middle gastric body (white arrowhead).

Right) Surveillance EGD. The same lesion was recognized (white arrowhead). The lesion was classified as perceptual error.

EGD, esophagogastroduodenoscopy

Supplementary Figure 5.

Left) Initial EGD. Initial early gastric cancer was recognized on the greater curvature of the antrum (white arrowhead). Missed cancer was not captured in the initial EGD images due to peristalsis.

Right) Surveillance EGD. An ulcer scar after endoscopic submucosal dissection was recognized on the greater curvature of the antrum (white arrowhead). A slightly pale and flat lesion was recognized on the lesser curvature of the antrum (green arrowhead). The lesion was classified as exposure error.

EGD, esophagogastroduodenoscopy

SUPPLEMENTARY TABLES

Supplementary Table 1. The list of MGCs that required surgery.

Lesion number	Treatment	Endoscopic cause	Histological type	Tumor size, (mm)	UL	Tumor depth	Ly	V	HM	VM
1	ESD and additional surgery	Perceptual error	Undifferentiated	42	0	SM2	0	0	0	0
2	ESD and additional surgery	Perceptual error	Undifferentiated	75	0	M	0	0	0	0
3	ESD and additional surgery	Perceptual error	Differentiated	12	0	SM2	0	0	0	0
4	Surgery	Inadequate preparation	Undifferentiated	25	1	M	0	0	0	0
5	Surgery	Perceptual error	Undifferentiated	26	0	M	0	0	0	0

MGC, missed gastric cancer; UL, ulcerative findings; Ly, lymphatic invasion; V, vascular invasion; HM, horizontal tumor margin; VM, vertical tumor margin; ESD, endoscopic submucosal dissection; M, mucosa; SM2, deep submucosa (tumor invasion is 500 μm or deeper from the muscularis mucosae)