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

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**Background and Aims:** Because 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 remain unclear. Therefore, we aimed to elucidate the endoscopic causes and characteristics of MGCs after ESD.

**Methods:** From January 2009 to December 2018, all patients undergoing ESD for initially detected EGC were enrolled. According to a review of 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:** Of 2208 patients who underwent ESD for initial EGC, 82 patients (3.7%) had 100 MGCs. The breakdown of 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 the incisura angularis (11 [48%]), posterior wall of the gastric body (6 [26%]), and antrum (5 [21%]).

**Conclusions:** We identified MGCs in 4 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. (Gastrointest Endosc 2023;98:735-43.)

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, because the entire stomach is preserved after ESD, there is a high risk of premalignant mucosae 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

*Abbreviations: CI, confidence interval; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; MGC, missed gastric cancer; OR, odds ratio.*

DIVERSITY, EQUITY, AND INCLUSION: We worked to ensure gender balance in the recruitment of human subjects. We worked to ensure sex balance in the selection of non-human subjects. While citing references scientifically relevant for this work, we actively worked to promote gender balance in our reference list. The author list of this paper includes contributors from the location where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.



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from .87% to 19.2%,[6-16] of which the rate of invasive MGC ranges from .4% to .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 causes of MGCs is limited. Identifying the endoscopic causes can contribute to the improvement of endoscopic examination quality. Therefore, we aimed to identify the endoscopic causes of MGCs and the characteristics associated with each endoscopic cause.

## 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. Patients who underwent additional gastrectomy after ESD and those who did not undergo surveillance EGD at Shizuoka Cancer Center were excluded. 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 no. 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 is 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, we performed a procedure modified from previously published screening protocols,[17-19] consisting of 35 endoscopic images. First, we took endoscopic images of the pylorus and 4 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, we took 3 endoscopic images (anterior wall, greater curvature, and posterior wall) from the fornix while the endoscope was inverted at the fornix. Then, we took endoscopic images of 3 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, 35 images were taken, 17 in the forward view and 18 in the retroflexion view. A lesion suspected to be gastric cancer was confirmed as cancer by biopsy sampling.

### Surveillance protocol after ESD

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

### Definitions

We defined MGC as gastric cancer diagnosed within 18 months after the initial ESD according to our institutional EGD surveillance protocol. We excluded cases of local recurrence. Endoscopic causes of MGCs were classified into the following 4 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 biopsy sampled 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 clinicopathologic information independently reviewed the endoscopic images taken according to the observation protocol during EGD before ESD and classified the endoscopic causes of MGCs. 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. We 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, as the 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

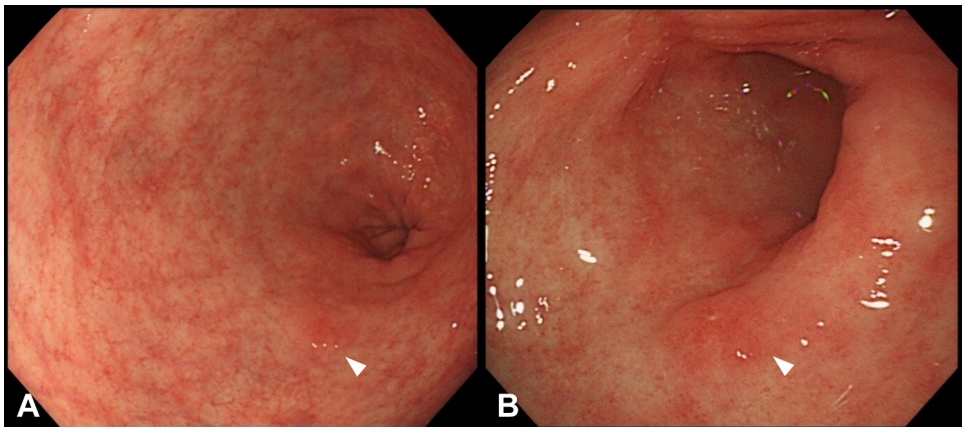


**Figure 1.** Representative images of perceptual error. **A,** Initial EGD. A reddish and slightly elevated lesion was recognized on the greater curvature of the antrum (*white arrowhead*). **B,** Surveillance EGD. The same lesion was recognized (*white arrowhead*) and was classified as a perceptual error.

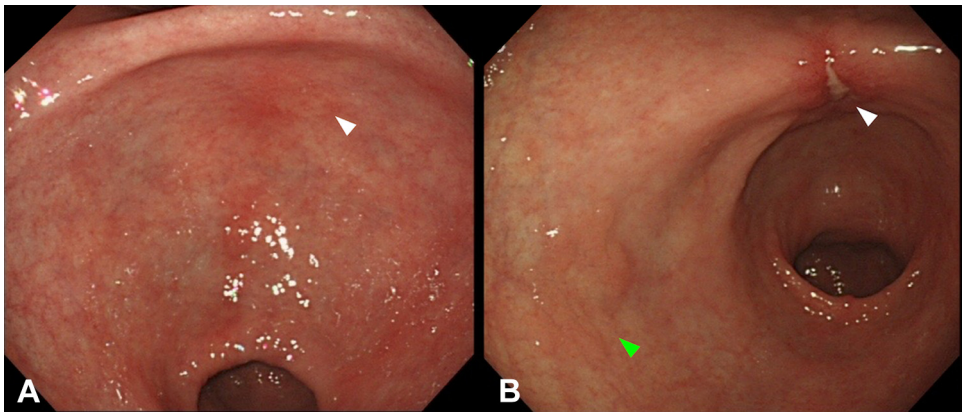


**Figure 2.** Representative images of exposure error. **A,** Initial EGD. An initial early gastric cancer was recognized on the lesser curvature of the antrum (*white arrowhead*). The missed cancer was not captured in the initial EGD images. **B,** Surveillance EGD. An ulcer scar after endoscopic submucosal 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.

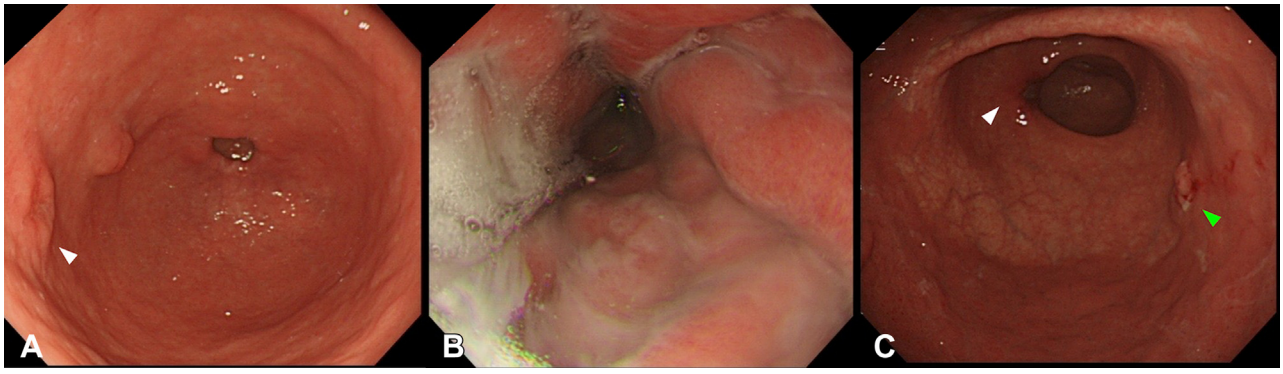


**Figure 3.** Representative images of inadequate preparation. **A,** Initial EGD. An initial early gastric cancer was recognized on the anterior wall of the antrum (*white arrowhead*). **B,** Initial EGD. A large amount of food residue or mucus remained and could not be removed. The gastric body was not easily visible. **C,** 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.

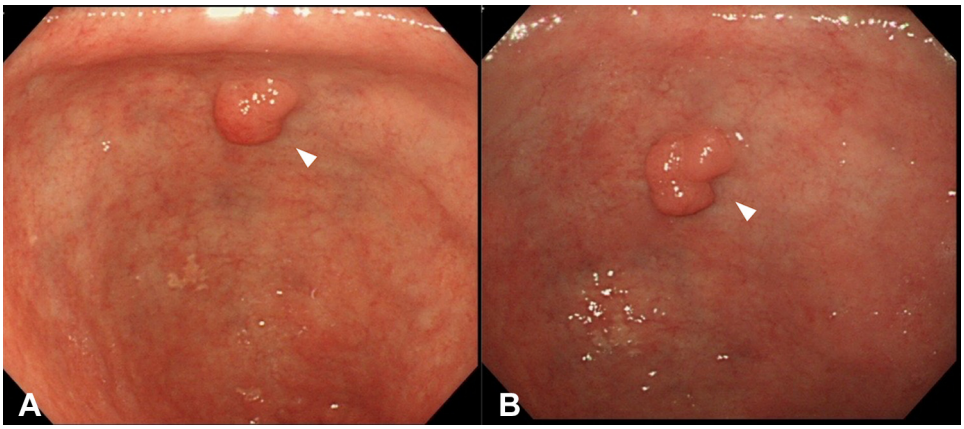


**Figure 4.** Representative images of sampling error. **A,** Initial EGD. A reddish and elevated lesion was recognized on the lesser curvature of the antrum (*white arrowhead*). The result of the biopsy sample was non-neoplastic in this EGD. **B,** Surveillance EGD. The same lesion was recognized (*white arrowhead*). The result of the biopsy sample was neoplastic in this EGD. This lesion was classified as a sampling error.

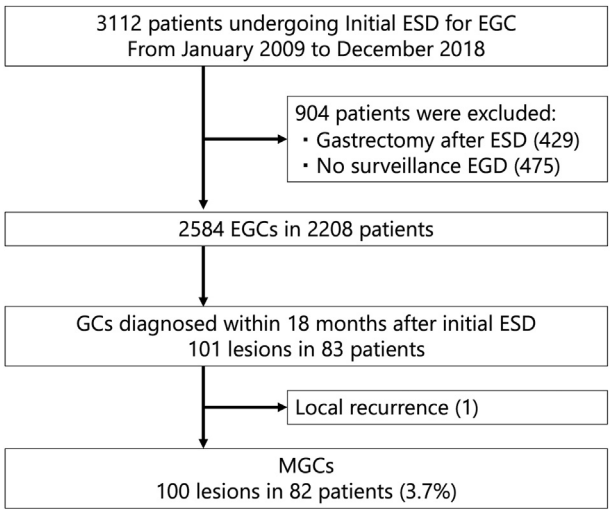


**Figure 5.** Patient flowchart. *ESD*, Endoscopic submucosal dissection; *EGC*, early gastric cancer; *GC*, gastric cancer; *MGC*, missed gastric cancer.

and 0-IIa+0-IIb; flat/depressed type, 0-IIb, 0-IIc, or a combination of these 2 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.

We classified the curability of endoscopic resections into endoscopic curability A, B, C-1, and C-2, according to the Japanese Gastric Cancer Association guidelines version 5.[2] Compared with past guidelines, endoscopic curability A and B corresponded to curative resection, whereas endoscopic curability C corresponded to noncurative resection. Among endoscopic curability C cases, those with histologic factors satisfying curative resection but with piecemeal resection or positive horizontal margin were subclassified as endoscopic curability C-1 and all other noncurative resections as endoscopic curability C-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 estimate the proportion of MGCs, classify the endoscopic causes of MGCs, identify the characteristics of MGCs in each endoscopic cause, and 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 the Student *t* test or Fisher exact test for univariate analysis. The lesion size cutoff 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 $P < .10$ on univariate logistic regression analysis using sex, age, *H 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 $P < .05$. All statistical analyses were performed using EZR (version 1.40; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[22]

# RESULTS

We identified 3112 patients who underwent ESD for initially detected EGC from January 2009 to December 2018. After reviewing the additional surgery and surveillance

**TABLE 1. Clinicopathologic characteristics of missed gastric cancers and initially detected early gastric cancers**

| | Missed gastric cancers (82 patients/100 lesions) | Initially detected early gastric cancers (2208 patients/2584 lesions) | *P* value |
|---|---|---|---|
| Patients | | | |
| Age, y | 73 (68-78) | 72 (66-78) | .399 |
| Sex | | | .051 |
| Male | 69 (84.1) | 1648 (74.6) | |
| Female | 13 (15.9) | 560 (25.4) | |
| *Helicobacter pylori* status | | | .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 | 12.5 (8-18) | 16 (10-25) | <.001 |
| Histologic type | | | .229 |
| Differentiated | 93 (93.0) | 2466 (95.4) | |
| Undifferentiated | 7 (7.0) | 118 (4.6) | |
| Depth | | | .779 |
| T1a (mucosa) | 93 (93.0) | 2322 (89.9) | |
| T1b1 (SM1) | 5 (5.0) | 168 (6.5) | |
| T1b2 (SM2) | 2 (2.0) | 90 (3.5) | |
| T2 (muscularis propria) or deeper | 0 | 4 (.1) | |
| Ulcerative findings | | | .701 |
| Negative | 94 (94.0) | 2385 (92.3) | |
| Positive | 6 (6.0) | 199 (7.7) | |
| Treatment | | | <.001 |
| Endoscopic submucosal dissection only | 95 (95.0) | 2584 (100) | |
| Surgery | 2 (2.0) | 0 (0) | |
| Endoscopic submucosal dissection and additional surgery | 3 (3.0) | 0 (0) | |
| Endoscopic curability | | | .105 |
| A | 90 (91.8) | 2236 (86.5) | |
| B | 5 (5.1) | 95 (3.7) | |
| C-1 | 0 (0) | 8 (.3) | |
| C-2 | 3 (3.1) | 245 (9.5) | |

Values are median (interquartile range) or n (%).
*SM1*, Superficial submucosa (tumor invasion <500 μm from the muscularis mucosae); *SM2*, deep submucosa (tumor invasion ≥500 μm from the muscularis mucosae).

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 1 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 clinicopathologic characteristics of the MGC and initially detected EGC are summarized in Table 1. The median lesion size of the MGC group was 12.5 mm (interquartile range, 8-18), which was significantly smaller than that of the initially detected EGC group.

## Incidence and endoscopic causes of 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).

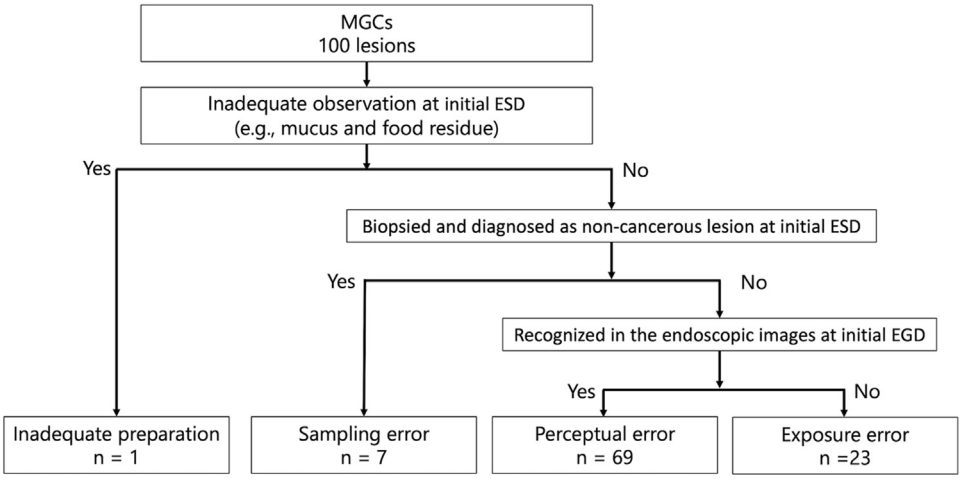


**Figure 6.** The algorithm to classify the endoscopic causes of MGCs. *MGC*, Missed gastric cancer; *ESD*, endoscopic submucosal dissection.

## 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). Lesions on the greater curvature were 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). No differences were found between trainees and experts in terms of perceptual error (20 trainees and 7 experts).

## Characteristics of exposure error

Of the 100 lesions of MGCs, 23 (23%) were attributed to exposure error. In 1 patient, endoscopic examination was not correctly performed according to our modified screening protocol. This examination was performed by a trainee. In the remaining cases, endoscopic examination was performed according to our modified screening protocol. The remaining 22 lesions were classified into 3 groups: posterior wall of the gastric body (6 [26%]), area around the incisura angularis (11 [48%]), and antrum (5 [21%]) (Table 3). In lesions with exposure errors found on the posterior wall of the gastric body, all endoscopic examinations before ESD were performed by trainees. Around the incisura angularis, 6 cases were examined by trainees and 5 cases by experts. On the antrum, 2 cases were examined by trainees and 3 cases by experts.

## Characteristics of MGCs required to undergo surgery

Five patients (5%) with MGCs required surgery because of the high risk of harboring lymph node metastasis. Four lesions were attributable to perceptual errors and 1 to inadequate preparation (Supplementary Table 1, available online at www.giejournal.org). Endoscopic images of MGCs requiring surgery are presented in Figure 3 and Supplementary Figures 1 to 4 (available online at www.giejournal.org).

# DISCUSSION

We 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, we found that lesion location in the greater curvature, isochromatic coloration, and smaller lesion size were risk factors for perceptual errors, whereas lesion location in 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 examination quality, it cannot completely eliminate missed lesions. Therefore, it is important to understand the most frequently occurring endoscopic errors. Herein we classified the endoscopic causes 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 causes of MGCs by retrospectively examining the associated endoscopic images. The strength of our study was that we were able to determine how cancers were missed and how this could have been counteracted by determining the characteristics of these errors.

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

| | | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | All lesions* | Perceptual error lesions n (%) | Odds ratio (95% confidence interval) | *P* value | Odds ratio (95% confidence interval) | *P* value |
| Sex | | | | | | |
| Female | 641 | 8 (1) | 1 (Ref) | | | |
| Male | 2012 | 61 (3) | 2.47 (1.18-5.20) | .019 | 2.45 (1.16-5.18) | .018 |
| Age | | | | | | |
| ≤72 y | 1308 | 34 (3) | 1 (Ref) | | | |
| >72 y | 1345 | 35 (3) | 1.00 (0.62-1.62) | .996 | | |
| *Helicobacter pylori* status | | | | | | |
| Eradicated | 425 | 8 (3) | | 1 (Ref) | | |
| Infected | 728 | 19 (2) | | 1.40 (.61-3.22) | .43 | |
| Naïve | 24 | 0 | | Not evaluated | | |
| Unknown | 1476 | 42 (3) | | 1.53 (.71-3.28) | .28 | |
| Site 1 | | | | | | |
| Upper third | 456 | 13 (3) | 1.28 (.65-2.53) | .474 | | |
| Middle third | 1080 | 31 (3) | 1.29 (.76-2.20) | .348 | | |
| Lower third | 1117 | 25 (2) | 1 (Ref) | | | |
| Site 2 | | | | | | |
| Lesser curvature | 1173 | 21 (2) | 1 (Ref) | | | |
| Anterior wall | 468 | 15 (3) | 1.82 (.93-3.55) | .081 | 1.75 (.88-3.43) | .106 |
| Greater curvature | 458 | 18 (4) | 2.24 (1.18-4.25) | .013 | 2.31 (1.21-4.40) | .011 |
| Posterior wall | 554 | 15 (3) | 1.54 (.78-2.98) | .216 | 1.51 (.77-2.91) | .233 |
| Macroscopic type | | | | | | |
| Elevated | 764 | 21 (3) | 1 (Ref) | | | |
| Flat/depressed | 1530 | 47 (3) | 1.12 (.67-1.89) | .665 | 1.02 (.60-1.74) | .944 |
| Excavated | 8 | 0 | Not evaluated | | | |
| Protruded | 143 | 0 | Not evaluated | | | |
| Mixed | 208 | 1 (0) | .17 (.02-1.27) | .084 | .16 (.02-1.21) | .076 |
| Coloration | | | | | | |
| Pale | 663 | 9 (1) | 1 (Ref) | | | |
| Reddish | 644 | 33 (2) | 1.83 (.87-3.84) | .118 | 1.74 (.82-3.72) | .150 |
| Isochromatic | 1346 | 27 (4) | 3.18 (1.48-6.82) | .002 | 3.17 (1.47-6.84) | .003 |
| Size | | | | | | |
| >12 mm | 1650 | 31 (2) | 1 (Ref) | | 1 (Ref) | |
| ≤12 mm | 1003 | 38 (4) | 2.06 (1.27-3.33) | .003 | 1.74 (1.07-2.84 ) | .026 |
| Endoscopist | | | | | | |
| Expert | 1433 | 37 (3) | 1 (Ref) | | | |
| Trainee | 1220 | 32 (3) | 1.02 (.63-1.64) | .947 | | |

*All lesions (n = 2653) are the sum of perceptual error lesions (n = 69) and initially detected early gastric cancer lesions (n = 2584).

Perceptual error was the most frequent type of error in this study. We 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, information is lacking on the coloration or location of cancers that are difficult to recognize; these characteristics are clarified in this study. We 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

**TABLE 3. Characteristics of exposure error**

| Lesion no. | 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 | Did not follow screening protocol |

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

synchronous EGC.[25] Therefore, 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 3 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 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 antrum could occur as human errors for any endoscopist, whereas 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 study reported that 75% of metachronous cancers were missed cancers.[27] More recent studies have reported on artificial intelligence for detecting EGC.[28-30] In the future, perceptual errors may be reduced using these artificial intelligence systems. For exposure errors, there is a technical aspect of whether or not the area can be delineated. Even in observing the entire stomach, some areas are prone to blind spots. Unless the area where the cancer exists is examined, the lesion cannot be detected even with the support of artificial intelligence. A study reported 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 etiologic classification of missed cancers. Thus, because videos were not reviewed, additional information other than that present in the images taken was lacking. Third, we 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, *H 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.

## DISCLOSURE

All authors disclosed no financial relationships.

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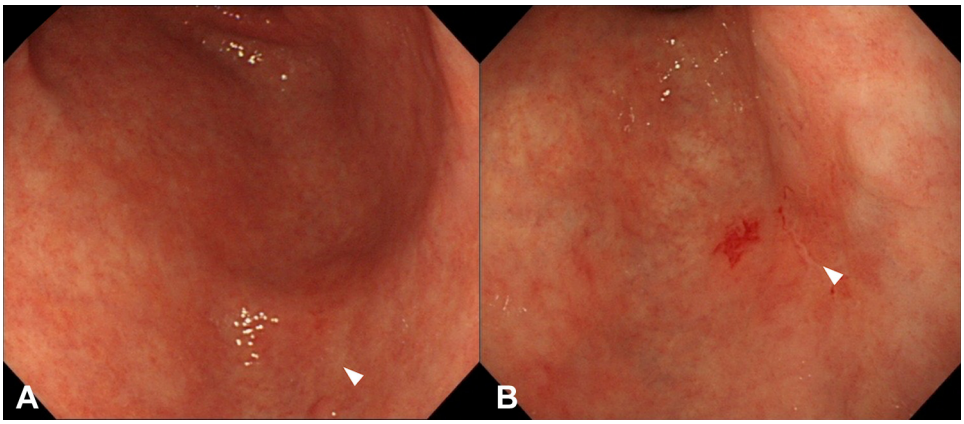
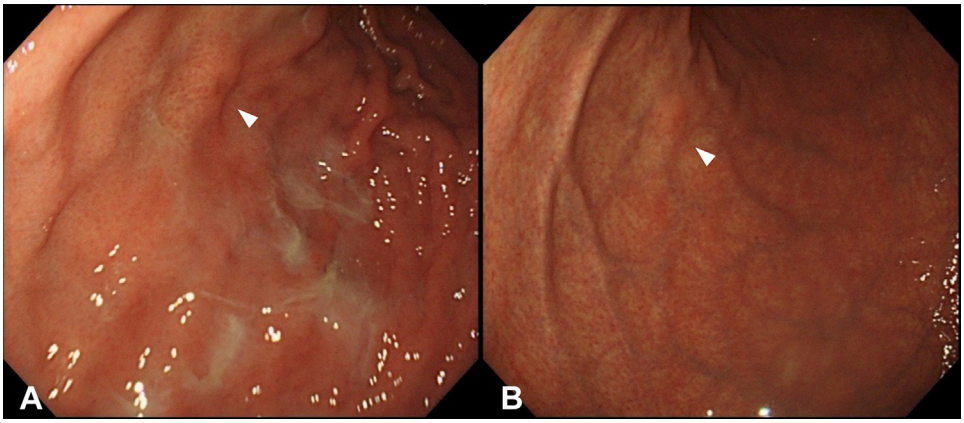
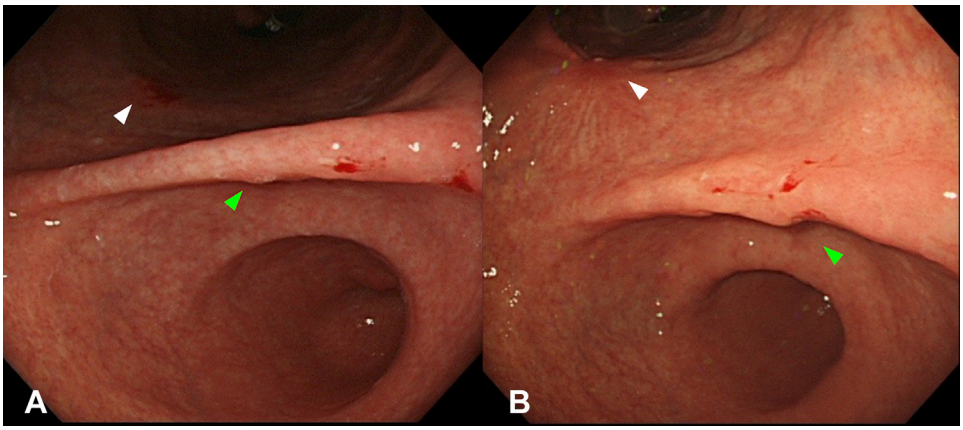


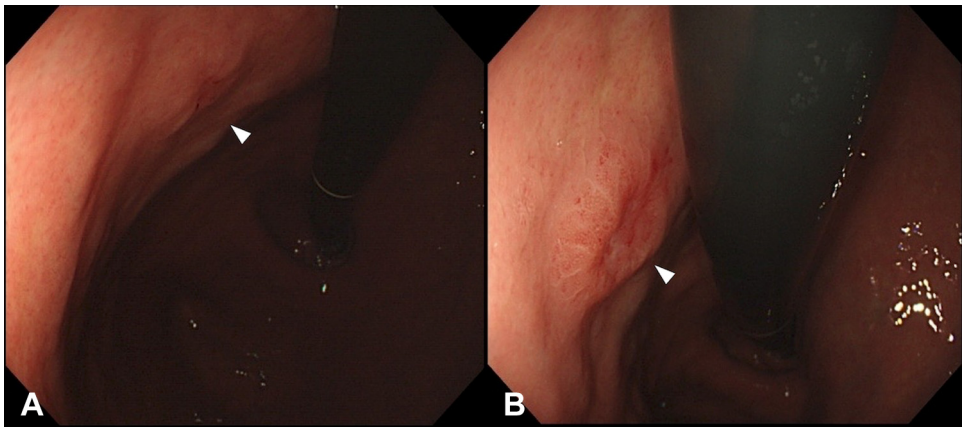

**Supplementary Figure 1. A,** Initial EGD. An isochromatic and flat lesion with rough membrane was recognized on the greater curvature of the lower gastric body (*white arrowhead*). **B,** Surveillance EGD. A slightly reddish and flat lesion was recognized on the same location (*white arrowhead*). The lesion was classified as a perceptual error.



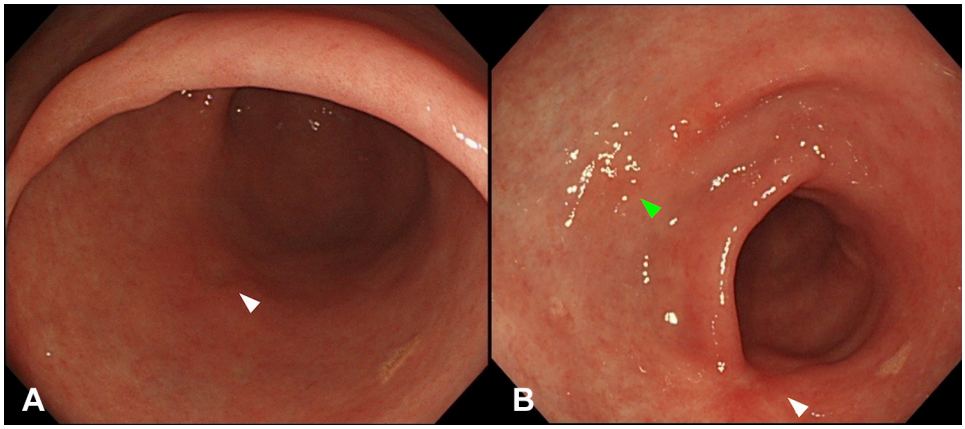

**Supplementary Figure 2. A,** Initial EGD. An isochromatic and slightly depressed lesion was observed on the anterior wall of the middle gastric body (*white arrowhead*). **B,** Surveillance EGD. The same lesion was recognized (*white arrowhead*) and was classified as a perceptual error.




**Supplementary Figure 3. A,** Initial EGD. An 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*). **B,** 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.




**Supplementary Figure 4. A,** Initial EGD. A lesion with a combination of slight elevation and depression was recognized on the anterior wall of the middle gastric body (*white arrowhead*). **B,** Surveillance EGD. The same lesion was recognized (*white arrowhead*) and was classified as perceptual error.




**Supplementary Figure 5. A,** Initial EGD. An initial early gastric cancer was recognized on the greater curvature of the antrum (*white arrowhead*). The missed cancer was not captured in the initial EGD images because of peristalsis. **B,** 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.

**SUPPLEMENTARY TABLE 1. Missed gastric cancers that required surgery**

| Lesion no. | Treatment | Endoscopic cause | Histologic type | Tumor size (mm) | Ulcerative findings | Tumor depth | Lymphatic invasion | Vascular invasion | Horizontal tumor margin | Vertical tumor margin |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 |

*ESD*, Endoscopic submucosal dissection; *M*, mucosa; *SM2*, deep submucosa (tumor invasion ≥500 from the muscularis mucosae).