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Original Article

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Clinical features of gastric adenoma detected within 3 years after negative screening endoscopy in Korea

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Abstract

Background: Early detection and management of gastric adenoma are important for preventing gastric cancer. The present study aimed to evaluate the predictors of missed gastric adenoma on screening endoscopy in Korea and identify the risk factors associated with interval precancerous gastric lesions.

Methods: All cases of gastric adenomas diagnosed via screening endoscopy between 2007 and 2019 were reviewed. Among them, those who had undergone endoscopy within 3 years were included in the present study. Missed gastric adenoma was defined as gastric adenoma diagnosed within 3 years after negative screening endoscopy.

Results: In total, 295 cases of gastric adenoma were identified. Of these, 95 (32.2%) were missed gastric adenoma cases (mean age, 60.6 years; average interval between final and index endoscopies, 12.6 months); the remaining 200 (67.8%) were newly detected adenoma cases. Univariate analysis revealed that male sex, endoscopist experience, observation time, and presence of gastric intestinal metaplasia (pathologically proven) were associated with missed gastric adenoma. Multivariate analysis revealed that gastric intestinal metaplasia (odds ratio [OR], 2.736; 95% confidence interval [CI], 1.320–5.667; $P = 0.007$) and shorter observation time of the index screening endoscopy (*B*, −0.011; OR, 0.990; 95% CI, 0.986–0.993; $P < 0.001$) were independent risk factors for missed gastric adenoma. The optimal cut-off for the observation time for detecting gastric adenoma was 3.53 minutes (area under curve, 0.738; 95% CI, 0.677–0.799; $P < 0.001$).

Conclusions: Gastric intestinal metaplasia is an indication of missed gastric adenoma. Therefore, careful inspection of gastric mucosa with gastric intestinal metaplasia and proper observation time can lower the possibility of missing the gastric adenoma during screening.

Keywords: gastric adenoma; screening endoscopy; gastric intestinal metaplasia; observation time

Introduction

Gastric cancer prevalence in South Korea is 10 times higher than that in the USA, with an age-adjusted annual incidence of 50–60 cases per 100,000 persons. However, regular health check-ups aid in the early diagnosis of gastric cancer; thus, the survival and cure rates in South Korea are high and mortality due to gastric cancer is decreasing [1]. Since 2002, nationwide screening endoscopy programs have been implemented for the early detection of precancerous lesions or gastric cancer. According to the adenoma–carcinoma sequence, gastric adenoma is a well-known precancerous lesion [2]. It begins with damage to the gastric mucosa induced by *Helicobacter pylori* infection and progresses to atrophic gastritis, intestinal metaplasia, low-grade adenoma/dysplasia, high-grade adenoma/dysplasia, and finally intestinal-type gastric cancer [3, 4].

Previous studies have focused on interval gastric cancer, which is gastric neoplasm detected within 2 or 3 years after negative screening endoscopy. The percentages of interval or missed gastric cancers among gastric cancers in Japan and Western countries are 13.1%–28.2% and 7.2%–14%, respectively [5, 6]. However, information on the missed rates and risk factors of missed gastric adenoma in other regions is needed. The causality of missed gastric adenoma is complex due to various factors, including adenoma characteristics, patient factors, pathologist factors, and endoscopist factors [2, 6].

Despite advances in endoscopic techniques, gastric adenoma can still be missed. Therefore, identifying complex risk factors associated with missed gastric adenoma is important. In the present study, the predictors of missed gastric adenoma on screening endoscopy in Korea were investigated and the risk factors associated with interval precancerous gastric lesions were identified.

Materials and methods

Study population

This study included patients who had undergone screening endoscopy at the Seoul National University Bundang Hospital (SNUBH) Health Promotion Center in Korea between 2007 and 2019, which provides various screening packages for the early detection of high-incidence cancers, including stomach, colon, liver, lung, breast, cervical, and prostate cancers. This retrospective

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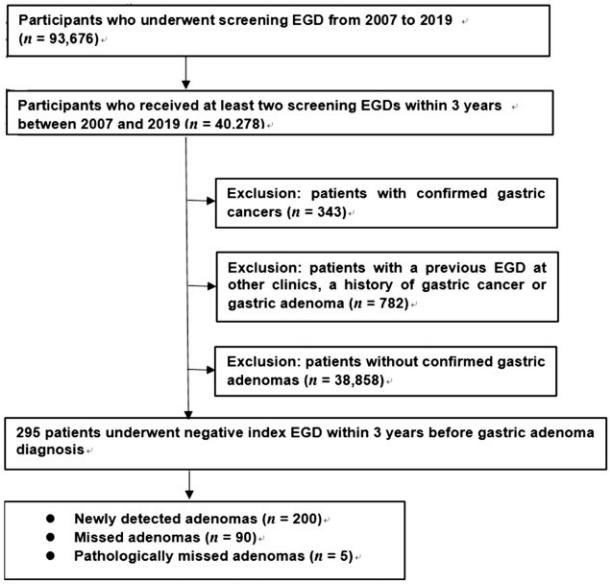

Figure 1. Flowchart of the patient selection process. EGD, esophagogastroduodenoscopy.

cross-sectional study included participants with gastric adenoma diagnosed via endoscopic biopsy after regular routine screening endoscopy. All screened participants volunteered or were employer-sponsored to undergo screening endoscopy regardless of age (including asymptomatic participants undergoing routine health check-ups). Patients with a previous endoscopy performed at other clinics and those with a history of gastric cancer or gastric adenoma were excluded (Figure 1).

Endoscopy was conducted by expert (>10 years of experience) and less-experienced (<3 years of experience) gastroenterologists certified by the Korean Society of Gastrointestinal Endoscopy using a high-resolution GIF-H260 or GIF-H290 video gastroscope (Olympus, Tokyo, Japan) and video systems (EVIS260 or 290 LUCERA; Olympus). In addition to conventional white-light endoscopy, narrow-band imaging was often used during the examination to further characterize the lesions. Endoscopically biopsied or resected specimens from patients with adenoma were evaluated based on the gross and histological features, presence of intestinal metaplasia, tumor size (width, length, and depth of invasion), *H. pylori* infection, and immunohistochemical staining (p53). The location of the adenoma on endoscopic findings was classified as the upper (cardia, fundus, and upper body), middle (mid-body, lower body, and angle), or lower (antrum and prepylorus) stomach. The presence of intestinal metaplasia is defined as a pathologic diagnosis of the gastric adenoma specimen of biopsy for screening or endoscopic mucosal resection/endoscopic submucosal dissection (EMR/ESD) for treatment by the pathologist. Therefore, the locations of intestinal metaplasia are the same as the sites of gastric adenoma [7, 8]. If patients showed positive results for endoscopic biopsy, rapid urease test, or urea breath test, they were confirmed to have *H. pylori* infection.

Clinicopathological features, including tumor factors and procedure-related factors, were reviewed from electronic medical records. The following data were collected: demographic data, endoscopic findings, adenoma location, adenoma pathology, the interval between the index and final endoscopies for adenoma detection and diagnosis, and procedure time of the index and final endoscopies. Similarly to previous studies, the observation time during endoscopy was calculated as the time from capturing the first endoscopic image in the duodenum to the last image in the esophagus [9, 10]. Observation time is defined as the time from capturing the first photo to the last photo using a reviewing picture archiving and communication system (PACS) with or without biopsy [9].

Missed gastric adenoma was defined as adenoma diagnosed within 3 years after a negative index screening endoscopy at the health promotion center (Figure 2). This retrospective cohort design included cases of missed adenoma and newly detected adenoma based on other references for missed gastric cancers in Western countries and Korea, and the definitions of missed adenoma and intervals were similar to those used in earlier studies [11–14]. The rate of missed adenomas was calculated as the number of missed adenomas divided by the total number of adenomas diagnosed. The interval of 3 years was set based on the doubling time of early gastric cancer of 2–3 years and slower progression of gastric adenoma (as a precancerous lesion) compared with early gastric cancer.

This study was approved by the Institutional Review Board of SNUBH (IRB No. B-2010–640-106). The requirement for written informed consent was waived due to the retrospective study design.

Statistical analysis

Data were analysed using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as percentage or mean ± standard deviation, and differences were calculated using Student's *t*-test. Differences in categorical variables were analysed using chi-square test or Fisher's exact test. Logistic regression analysis was used to estimate the association between missed adenomas and clinicopathological features. Only factors with *P*-values of <0.05 in univariate analysis were subsequently used in logistic regression multivariate analysis and are presented as odds ratio (OR) and 95% confidence interval (CI). All two-sided *P*-values of <0.05 were considered statistically significant. The cut-off value for the procedure time in the prediction of gastric adenoma was defined as the value with the highest Youden index (sensitivity + specificity − 1) [11].

Results

Baseline clinical characteristics

In total, 295 patients were diagnosed with gastric adenoma, including 95 (32.2%) with missed adenomas and 200 (67.8%) with newly detected adenomas. The mean (± standard deviation) age of the patients was 60 (± 9) years and 75% of the patients were male. To investigate the predictors of missed adenoma, the demographics and baseline characteristics of index screening endoscopy between missed adenoma and newly detected adenoma cases were compared (Tables 1 and 2). For missed adenoma cases, the proportion of male patients (81.1% vs 72.5%, $P < 0.001$), examination conducted by less-experienced endoscopists (22% vs 12%, $P = 0.020$), and presence of intestinal metaplasia in gastric mucosa cases (84.6% vs 76.3%, $P = 0.045$) were significantly higher than those in newly detected adenoma cases, whereas the mean observation time during index screening endoscopy was significantly shorter (3.00 vs 4.38 minutes, $P < 0.001$) in gastric mucosa cases than that in newly detected adenoma cases. No significant differences were found between the two groups in terms of age, tumor location, tumor size, *H. pylori* infection, p53 expression,

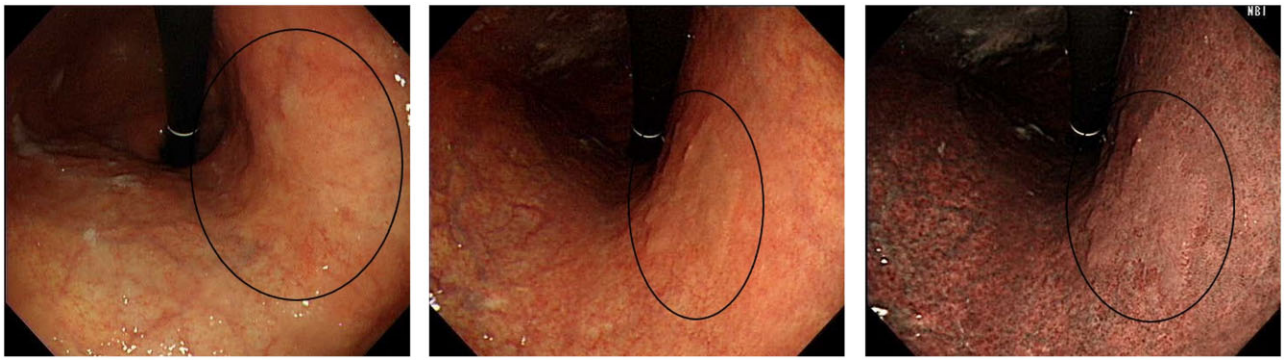

Figure 2. Endoscopic findings of missed gastric adenoma. (A) On the first endoscopic examination (screening endoscopy), a 3.0-cm round nodular lesion was observed in the lesser curvature of the mid-body (black circle). (B) Thirty months after the first endoscopic examination, a similar round nodular lesion was observed at the same location (black circle). (C) Narrow-band image (black circle).

Table 1. Demographic and endoscopic characteristics of 295 patients in the missed adenoma and newly detected adenoma groups

Characteristic	Missed adenomas ($n = 95$)	Newly detected adenomas ($n = 200$)	P-value
Age, mean ± SD, years	60.6 ± 10.4	60.3 ± 9.2	0.770
Gender			
Male	77 (81.1)	145 (72.5)	0.045*
Female	18 (18.9)	55 (27.5)	
Family history of gastric cancer	21 (22.6)	43 (21.5)	0.518
Endoscopist experience			
>10 years	74 (77.9)	176 (88.0)	
<3 years	21 (22.1)	24 (12.0)	0.020*
Procedure time of the index endoscopy, mean ± SD, minutes	3.00 ± 1.62	4.38 ± 1.87	<0.001*
Sedation	91 (95.7)	245 (96.0)	0.780*

Data are presented as *n* (%) unless otherwise indicated. SD, standard deviation. *$P < 0.05$.

Table 2. Clinicopathological features of missed and newly detected adenomas

Feature	Missed adenomas ($n = 95$)	Newly detected adenomas ($n = 200$)	P-value
Location in the stomach			0.957
Upper	11 (11.6)	20 (10.0)	
Middle	39 (41.1)	74 (37.0)	
Lower	45 (47.4)	106 (53.0)	
Size, mean ± SD, mm			
Width	8.4 ± 6.3	9.2 ± 6.4	0.423
Length	6.2 ± 4.6	6.8 ± 4.4	0.342
Depth	0.089 ± 0.22	0.095 ± 0.063	0.454
Helicobacter pylori	36 (40.9)	80 (46.0)	0.510
Intestinal metaplasia	77 (84.6)	129 (76.3)	0.045*
p53 expression	4 (6.8)	12 (10.3)	0.318
Pathology	253 (26.1)	72 (30.1)	0.360
LGD	81 (85.3)	175 (87.5)	
HGD	14 (14.7)	25 (12.5)	
Treatment			0.985
No	25 (26.3)	47 (23.5)	
Yes (EMR, ESD, or APC)	70 (73.7)	153 (76.5)	

Data are presented as *n* (%) unless otherwise indicated. LGD, low-grade dysplasia; HGD, high-grade dysplasia; SD, standard deviation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal resection; APC, argon plasma coagulation. *$P < 0.05$.

tumor pathology (low- or high-grade dysplasia), treatment, or sedation.

Pathological findings of missed adenoma and newly detected adenoma

The antrum (47.4%) was the most common site for the occurrence of missed adenoma; the occurrence rate of missed adenoma was lower than that of newly detected adenoma (53.0%). However, the occurrence rate of missed adenoma was higher than that of newly detected adenoma in other locations (angle, low body, and upper body of the stomach). The mean size of missed adenoma was 8.4 mm, whereas that of newly detected adenomas was 9.2 mm (Table 2). The interval between the index and final endoscopies (i.e. diagnosis) in the missed adenoma group was within 1 year (nearly 1 year) in 26%, 1–2 years in 54%, and 2–3 years in 20% of the patients. The occurrence rate of

intestinal metaplasia in gastric mucosa was significantly higher in the missed adenoma group than in the newly detected adenoma group (84.6% vs 76.3%, $P = 0.045$).

No significant difference was found in the incidence of *H. pylori* infection on biopsy or endoscopically resected specimens between missed adenoma and newly detected adenoma cases (40.9% vs 46%, $P = 0.510$). Furthermore, no significant difference was observed in p53 expression between the missed adenoma and newly detected adenoma groups (6.8% vs 10.3%, $P = 0.318$). The rates of high-grade dysplasia were 14.7% for missed adenoma cases and 12.5% for newly detected adenoma cases (Table 2).

Multivariate logistic regression analysis for factors associated with missed adenoma

Predictors with *P*-values of <0.1 in the univariate analysis were included in multivariate logistic regression analysis. The results of the multivariate logistic regression analysis for missed adenoma are shown in Table 3. Histologically proven intestinal metaplasia of gastric mucosa was associated with an increased risk of missed adenoma (*B*, 1.006; OR, 2.736; 95% CI, 1.320–5.667; $P = 0.007$). A shorter observation time during index screening endoscopy was also a significant risk factor for missed adenoma (*B*, −0.011; OR, 0.990; 95% CI, 0.986–0.993; $P < 0.001$).

Cut-off observation time for the prediction of missed adenoma

The results of the receiver-operating characteristic curve analysis were used to determine the optimal cut-off observation time during index endoscopy and predict the risk of missed adenoma during the study period. For all patients enrolled, the optimal cut-off value was 3.53 minutes, for which the area under the curve was 0.738 (95% CI, 0.677–0.799; $P < 0.001$). The sensitivity and specificity for the prediction of the risk of missed adenoma were 62% and 74%, respectively.

For 95 patients with missed adenoma, the average observation time for the index endoscopy was 3 minutes, which was shorter than the average time for the final diagnostic endoscopy (4.38 minutes).

Discussion

Most studies on gastric cancer have examined missed or interval gastric cancer; however, the rates and predictors of missed gastric adenoma have not been established. In the present study, the presence of gastric intestinal metaplasia and adequate observation time (>3.53 minutes) were identified as significant predictors of missed gastric adenoma.

Patients with gastric adenoma are predominantly male and are ~10 years younger than patients with gastric cancer (61.35 vs 70 years) [12]. The incidences of adenoma are 0.5%–3.75% in Western countries and 9%–20% in regions with a high incidence of gastric cancer in Asian countries, such as Korea and Japan [3, 13]. Gastric adenoma can occur anywhere in the stomach but is most commonly found in the antrum. Most gastric adenomas are diagnosed incidentally during screening endoscopy. Gastric adenoma is an abnormal change originating from gastric epithelial cells and is a precursor of gastric cancer. Progression to cancer is associated with the degree of dysplasia. Approximately 11% of gastric adenoma cases progress to gastric cancer within 4 years of follow-up [7, 14]. Although not all patients with gastric adenoma progress to gastric cancer, biopsy alone cannot predict this and, in many cases, adenoma or early gastric cancer after endoscopic resection was more advanced than that at the first biopsy [8]. Therefore, we must improve the quality of screening endoscopy by assessing the rates and risk factors of missed gastric adenoma [15].

In the present study, intestinal metaplasia of the gastric mucosa was associated with a 3-fold increased risk of missed adenoma. In accordance with the findings of a recent South Korean study [16], patients with biopsy-proven intestinal metaplasia in the background or surrounding gastric mucosa were at a higher risk of gastric adenoma. Severe metaplastic progression was observed in 146 patients with endoscopically resected gastric adenoma or early gastric cancer. In addition, similar background mucosal changes were found in the adenoma and early gastric cancer groups.

A nationwide South Korean survey found that the incidence of endoscopic intestinal metaplasia was 12.5%; however, this was observed in specimens diagnosed by health check-up endoscopy, not by histology [17]. Another South Korean study indicated that the incidence of intestinal metaplasia in the antrum was 28.6% [18]. This condition is a well-known precancerous change on screening endoscopy that can lead to the adenoma–carcinoma sequence. The results of the present study are in agreement with those of previous studies that evaluated the risk factors of interval early gastric cancer [19, 20]. Gastric intestinal metaplasia is also a risk factor for interval early gastric cancer [19]. According to the management of epithelial precancerous conditions and lesions in the stomach (MAPS II) guidelines, patients with intestinal metaplasia are at risk for gastric cancer. However, the importance of risk stratification for these patients has been underestimated. In high-risk regions, such as Japan and Korea, identification and surveillance of patients with precancerous gastric conditions (intestinal metaplasia) are cost-effective [21].

In the present study, which included a large number of participants over a 13-year period, the optimal observation time during screening endoscopy for detecting gastric adenoma was 3.53 minutes. Theoretically, a longer observation time is better for successfully detecting abnormal lesions; however, time is limited in clinical practice. The results of the present study are consistent with those of a previous study reporting that endoscopists taking longer procedure times (>7 minutes) were three times more likely to detect gastric cancer [10]. Kawamura *et al.* [22] reported that the detection rate of neoplastic lesions did not differ significantly between endoscopists with moderately long (5–7 minutes) and long

Table 3. Multivariate analysis for risk factors of missed adenoma

Factor	*B*	Adjusted odds ratio	95% confidence interval	*P*-value
Male gender	0.463	1.588	0.784–3.219	0.199
Endoscopist experience (<3 years)	0.545	1.725	0.817–3.642	0.153
Intestinal metaplasia	1.006	2.736	1.320–5.667	**0.007**
Observation time of index endoscopy	−0.011	0.990	0.986–0.993	**<0.001**

Bold menas p-value < 0.05, statistically significant.

(>7 minutes) observation times, indicating that adequate observation time during screening endoscopy is necessary in successfully detecting precancerous lesions, such as gastric adenoma. The present study compared the procedure time between index and final screening endoscopies and identified the optimal observation time for lowering the chances of missing gastric adenoma during screening.

Gastric adenoma is very difficult to diagnose during screening endoscopy because the surfaces and margins of adenomas are subtle and ill-defined, thereby increasing the rate of missed diagnoses [23]. In the present study, the average size (width, 8.4 mm; length, 6.2 mm) of the missed adenomas was smaller than that reported in previous studies [3, 8, 24]. The average sizes of missed adenomas and newly detected adenomas were <10 mm, confirming that the screening endoscopy at our health promotion center is a high-quality examination. Several studies have reported that the average size of endoscopically resected adenomas is >10 mm, with some exceeding 20 mm [8, 24]. However, the widths and lengths of the missed adenomas (width, 2–35 mm; length, 1–20 mm) and newly detected adenomas (width, 2–38 mm; length, 2–25 mm) varied. Nevertheless, the minimum and average widths did not vary significantly (width: 2 vs 2 mm; length: 8 vs 9 mm). Both highly experienced and less-experienced endoscopists could detect gastric adenomas smaller than the reported average sizes; therefore, my results suggest that the optimal procedure time identified in my study is a good marker for the early detection of gastric adenoma.

The quality of endoscopy is important because the diagnostic rate is an endoscopist-dependent factor. The adenoma detection rate, cecal intubation rate, and withdrawal time are representative quality indicators of colonoscopy. In contrast to colonoscopy, no gold-standard quality indicators have been established for upper endoscopy [25]. The present study suggests that the observation time during index endoscopy and presence of intestinal metaplasia in biopsied or resected adenoma specimens are good indicators of the endoscopist's experience level. Most adenomas (76.5%) were endoscopically treated (EMR, ESD, or argon plasma coagulation) at our institution, whereas the remaining 23.5% adenomas were treated at other tertiary hospitals, lost to follow-up, or contraindicated for the procedure due to old age or long-term regular follow-up due to small size without endoscopic resection.

Gastric adenoma has a slower progression rate than gastric cancer. In this study, the majority of missed adenomas were low-grade dysplasia; thus, it can be concluded that adenomas with low-grade dysplasia are more frequently and easily missed than adenomas with high-grade dysplasia (85.3% vs 14.7%). As reported previously [15, 25, 26], several reasons are implicated in missing adenoma during endoscopy: inability to detect lesions; detecting lesions but not performing biopsies; taking an insufficient number of or poor-quality biopsy specimens; no appropriate follow-up after a normal endoscopy; technical limitations in visualizations of specific areas; and inability to identify early neoplastic conditions. Furthermore, poor patient compliance during esophagogastroduodenoscopy (EGD) and pathologist mistakes may contribute to the failure of the diagnosis of gastric adenoma. Other contributing factors for missed adenoma are marked gastric atrophy and presence of intestinal metaplasia [6, 19, 20, 27]. To reduce the occurrence rate of missed adenoma during gastroscopy, close observation for the presence of intestinal metaplasia of the gastric mucosa should be performed. In addition, if a lesion is suspected, a proper biopsy using narrow-band imaging or washout of the residual secretions should be performed immediately. Furthermore, clinicians should be aware of the most common locations of gastric cancer in advance and spend a longer observation time in these areas.

This study has several strengths. First, the observation times during the index (3 minutes) and final endoscopies (4.38 minutes) were compared for missed adenoma. Second, the same endoscopists (>10 years of experience) performed screening endoscopy at a single health promotion center during the 13-year study period. Third, the same sedation method (midazolam with or without pethidine) and the same types of endoscopes (Olympus H260 or H290) were used for all participants. Fourth, all screening endoscopy PACS images were stored in the SNUBH BestCare System (electronic medical records), which allows the reviewing of images at any time. Fifth, biopsy-proven intestinal metaplasia was analysed in this study.

However, this study also has some limitations. First, this is a retrospective study. An actual observation time was not obtained. The calculated observation time was not actual, but theoretical; the actual observation time was longer than the calculated observation time of 3.53 minutes. Second, this study did not evaluate the effect of lifestyle factors, such as alcohol consumption or smoking status, on gastric adenoma. Third, each endoscopist had a different style of capturing the first and last images. Therefore, differences may exist between the actual and calculated observation times obtained by reviewing the images recorded by each endoscopist. Therefore, the actual observation time is slightly longer than the suggested or calculated time. Fourth, the data obtained during the 13-year study period were mostly derived using GIF-H260 or GIF-H290; thus, very limited data were obtained using narrow-band imaging or indigo carmine. Fifth, a selection bias for the endoscopic observation time may exist. Severe gastric intestinal metaplasia cases may have been observed for longer times and biopsy would have been performed, which would have thus increased the endoscopic examination times.

In conclusion, the present study showed that intestinal metaplasia in background gastric mucosa and a relatively short observation time during endoscopy (<3.53 minutes) are positively associated with missed gastric adenoma. The key points to overcome missed gastric adenomas are careful endoscopy observation, particularly in identifying intestinal metaplasia, and sufficient observation times during endoscopy.

Authors' Contributions

H.Y.K. contributed to the data design, research, and analyses, and wrote the manuscript. The author read and approved the final version of this article.

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available from the corresponding author on reasonable request. Patient consent for publication was not required.

Conflict of Interest

None declared.

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