Correlation between Endoscopic and Histological Diagnoses of Gastric Intestinal Metaplasia

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Background/Aims: Intestinal metaplasia (IM) is a premalignant condition. This study aimed to evaluate the correlation between endoscopic and histological findings of IM. **Methods:** The cases of IM were graded by conventional endoscopy, and biopsies were taken from the antrum and body of 1,333 subjects for histological IM diagnosis. Multivariate analyses were performed to identify the factors that affect the sensitivity of endoscopic IM diagnosis. **Results:** The sensitivity/specificity of endoscopic IM diagnosis based on histology was 24.0%/91.9% for the antrum and 24.2%/88.0% for the body. As indicated by multivariate analysis, the presence of endoscopic atrophic gastritis (AG) (odds ratio [OR], 4.73; 95% confidence interval [CI], 2.07 to 10.79) and the activity of mucosal inflammation (OR, 2.21; 95% CI, 1.08 to 4.54) were associated with the sensitivity of endoscopic IM diagnosis in the antrum, while the presence of endoscopic AG (OR, 8.02; 95% CI, 4.55 to 14.15), dysplasia (OR, 2.40; 95% CI, 1.07 to 5.39), and benign gastric ulcers (OR, 0.35; 95% CI, 0.15 to 0.081) were associated with the sensitivity of endoscopic IM diagnosis in the body. **Conclusions:** As the sensitivity of endoscopic IM diagnosis was low, a high index of suspicion for IM is necessary in the presence of atrophy, and confirmation by histology is also necessary. **(Gut Liver 2013;7:41-50)**

Key Words: Diagnosis; Endoscopy; Histology; Intestinal metaplasia

INTRODUCTION

The Correa hypothesis postulates that gastric carcinogenesis is a multistep process starting with the development of chronic gastritis to atrophic gastritis (AG) and intestinal metaplasia (IM), then to dysplasia, and finally to cancer.[1] IM is thought to be a premalignant lesion of the stomach in which the normal gastric mucosa is replaced by mucosa which resembles that of the intestine.[2] The most widely used classification of IM was proposed by Jass and Felipe.[3] In addition, there are a few studies which identified possible cancer risks and specific subgroups of IM (complete and incomplete types).[4-6] For example, incomplete-type metaplasia has been reported to be significantly correlated with some topographic patterns of metaplasia associated with greater cancer risk.[7] However, other studies refuted this idea[8] and recommended the establishment of clear guidelines for follow-up or treatment of patients with IM.[9] Recently, a new staging system for gastritis has been proposed to identify patients at the highest risk for gastric cancer.[10,11] Furthermore, risk scores for clinical, histological, and serologic parameters which can predict the presence of extensive intragastric IM with increased risk of gastric cancer have also been proposed.[12,13] However, these methods have not been used widely. Thus, the follow-up frequency and treatment of these patients varies widely in clinical practice.

The prevalence of *Helicobacter pylori* infection and gastric cancer is unacceptably high in South Korea. Seroprevalence of *H. pylori* was 59.6% among asymptomatic South Korean adults in 2005[14] and the age-standardized incidence of gastric cancer during 2003 to 2005 in South Korea was 64.2 per 100,000 person-years for men and 25.4 for women.[15] IM is frequently encountered when performing upper gastrointestinal endoscopy in South Korea but cases of this condition need to be confirmed by biopsies.[16] It would be convenient if endoscopic diagnosis of

IM is possible. However, IM is known to be difficult to recognize endoscopically[17] even with chromoendoscopic techniques using methylene blue and indigo carmine. Therefore, it is very important to understand the correlation between endoscopic and histological findings of IM. However, only few studies on this topic have been performed.[18-20] Based on this background, the current study was designed to evaluate the sensitivity and specificity of endoscopic diagnosis of IM, and factors that may affect the diagnosis.

MATERIALS AND METHODS

1. Subjects

A total of 1,333 subjects who visited Seoul National University Bundang Hospital for upper gastrointestinal endoscopy from September 2003 to March 2007 were consecutively enrolled in this study. About 50% had experienced gastrointestinal symptoms such as epigastric pain, discomfort, soreness, bloating, or indigestion within 3 months of enrollment. The patients requested endoscopy with *H. pylori* testing for gastric cancer screening. The subjects were categorized into a control group and four different disease groups. The control group consisted of subjects who had only mild gastritis or normal endoscopic findings without any evidence of significant gastroduodenal disease. The four disease groups were duodenal ulcer (DU), benign gastric ulcer (BGU), dysplasia, and gastric cancer. Patients in these groups were categorized according to endoscopic- and histological-based diagnoses. Patients with a history of any stomach surgery, *H. pylori* eradication therapy, systemic diseases for which medication was taken for a long period of time, or use of a proton pump inhibitor within 2 weeks of enrollment were excluded from the study. The Institutional Review Board at Seoul National University Bundang Hospital approved this study, and written informed consent was obtained from all participants.

2. Endoscopic examinations

The patients were required to fast at least for 6 hours before undergoing the endoscopic procedure. Endoscopy was performed using a GIF-Q260 (Olympus Co., Tokyo, Japan). All endoscopic procedures were performed by a single experienced endoscopist (N. Kim) to minimize interobserver variability. The presence of AG was characterized by well visualization of the submucosal vessel due to thinning of the mucosa in the antrum and body. The presence of IM was determined by whitish color change with plaques, patches, or homogeneous discoloration on the gastric mucosa.[18] The endoscopic IM grade was divided into three categories. Grade I was defined as metaplastic mucosa with fine or granular plaques. Grade II was characterized by coarse plaques or patches. Grade III was defined as cases with more coarse and larger plaques or patches.[19]

3. Histological examination and *H. pylori* testing

To determine the presence of current *H. pylori* infection, 10 biopsy specimens were taken for three types of *H. pylori* testing (histology, rapid urease testing, and culture). Two biopsy specimens were taken from the greater curvature of both the antrum and body of the stomach and three were from both the lesser curvature of the antrum and body (Fig. 1). Among the 10 specimens, two from the antrum and two from the body were fixed in formalin, and assessed for the presence of *H. pylori* by modified Giemsa staining. The degree of inflammatory cell infiltration (activity and chronic inflammation), atrophy (loss of appropriate glands including both metaplastic and nonmetaplastic atrophy), and metaplasia were determined by hematoxylin and eosin (H&E) staining. The histological features of the gastric mucosa were recorded using the updated Sydney scoring system (i.e., 0, none; 1, mild; 2, moderate; and 3, marked);[21] the score of the biopsy specimens from the greater and lesser curvature of the stomach were averaged. All biopsies were examined independently by two experienced pathologists (H.S. Lee and G. Choe) who were unaware of the clinical study details. In the event of disagreement, the biopsies were re-examined by these two pathologists until agreement was reached. When the specimens were prepared so that the full thickness of the gastric mucosa could not be evaluated due to problems such as improper fixation, inaccurate orientation, or inappropriate sections, or if inflammation prevented clear distinction between nonatrophic and atrophic phenotypes, the samples were classified as indefinite for atrophy and excluded from the study.

One specimen each from the lesser curvature of the antrum and body (Fig. 1) was used for rapid urease testing (CLOtest; Delta West, Bentley, Australia). The result of rapid urease testing

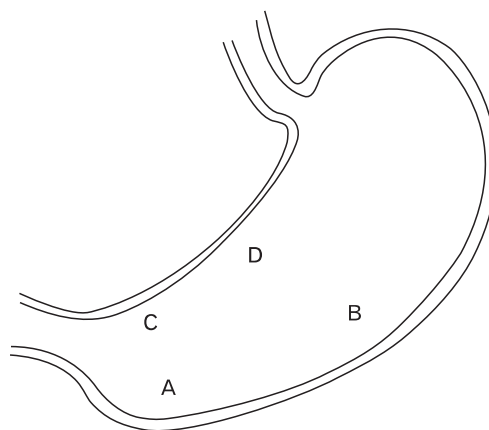**Fig. 1.** The description of the biopsy sites. Histology and cultures were performed on the two specimens A and C, each from the antrum, and on the two specimens B and D, each from the body. In addition, rapid urease testing was performed on one specimen each from C and D. A, the greater curvature of mid antrum; B, the greater curvature of mid body; C, the lesser curvature of mid antrum; D, the lesser curvature of mid body.

was finally read after 24 hours. Two specimens from the antrum and body were used for *H. pylori* culture (Fig. 1). The antral and body biopsy specimens were evaluated separately. The presence of *H. pylori* was determined by Gram staining, colony morphology; and positive oxidase, catalase, and urease reactions.[22] If any of these three *H. pylori* tests were positive, the patient was regarded as having an on-going *H. pylori* infection.

4. High iron diamine and alcian blue, pH 2.5 (HID-AB2.5) staining for IM subtyping

Sulfated (brown) and acidic nonsulfated (blue) mucosubstances were simultaneously stained with HID-AB2.5. Cases of IM were classified as follows: type I, mature absorptive cells and goblet cells, the latter secreting sialomucins; type II, few or absent absorptive cells, presence of columnar 'intermediate' cells

Table 1. The Baseline Characteristics of 1,333 Subjects Based on Endoscopic IM Status

Characteristic	Endoscopic IM absent (n=1,114)	Endoscopic IM present (n=219)	Total (n=1,333)	p-value
Age, yr	56.9±13.4	61.6±10.1	57.7±13.0	<0.001*
Age intervals				<0.001*
≤29	26 (100)	0 (0)	26 (2.0)	
30-39	95 (94.1)	6 (5.9)	101 (7.6)	
40-49	210 (92.1)	18 (7.9)	228 (17.1)	
50-59	270 (83.3)	54 (16.7)	324 (24.3)	
60-69	326 (78.2)	91 (21.8)	417 (31.3)	
≥70	187 (78.9)	50 (21.1)	237 (17.8)	
Gender				0.040*
Male	639 (81.8)	142 (18.2)	781 (58.6)	
Female	475 (86.1)	77 (13.9)	552 (41.4)	
Smoking				0.084
Never	520 (85.7)	87 (14.3)	607 (46.2)	
Past	363 (82.5)	77 (17.5)	440 (33.5)	
Current	214 (79.9)	54 (20.1)	268 (20.4)	
Alcohol				0.773
Never	370 (83.3)	74 (16.7)	444 (33.9)	
Past	156 (85.2)	27 (14.8)	183 (14.0)	
Current	568 (83.0)	116 (17.0)	684 (52.2)	
Disease				<0.001*
Control	292 (85.9)	48 (14.1)	340 (25.5)	
DU	138 (92.0)	12 (8.0)	150 (11.3)	
BGU	151 (89.3)	18 (10.7)	169 (12.7)	
Gastric cancer	431 (81.8)	96 (18.2)	527 (39.5)	
Dysplasia	102 (69.4)	45 (30.6)	147 (11.0)	
Helicobacter pylori infection				0.327
Negative	193 (85.8)	32 (14.2)	225 (16.9)	
Positive	921 (83.1)	187 (16.9)	1,108 (83.1)	
Serologic features				
PG I, ng/mL	59.5±41.4	63.3±47.8	60.1±42.4	0.267
PG II, ng/mL	17.9±13.0	20.1±13.8	18.2±13.1	0.038*
PG I/II ratio	3.9±2.1	3.6±3.1	3.8±2.3	0.119
Hemoglobin, g/dL	12.7±2.4	13.0±2.3	12.7±2.4	0.086
Albumin, g/dL	4.0±0.7	4.0±0.6	4.0±0.7	0.657
C-reactive protein, ng/dL	4.2±5.3	3.7±4.8	4.1±5.2	0.459

Data are presented as mean±SD or number (%).
IM, intestinal metaplasia; DU, duodenal ulcer; BGU, benign gastric ulcer; PG, pepsinogen.
*Statistical significance.

in various stages of differentiation secreting neutral and acid sialomucins and goblet cells secreting sialomucins or, occasionally, sulfomucins, or both; and type III, columnar intermediate cells secreting predominantly sulfomucins and goblet cells secreting sialomucins, sulfomucins, or both. If more than one HID subtype of IM was present, the specimen was classified based on the predominant IM phenotype.

5. Serum pepsinogen (PG) levels and biochemistry

Fasting serum was collected from all subjects at the time of study entry. The samples were centrifuged immediately at 4°C and stored at -70°C until use. Serum concentrations of pepsinogen I and II were measured using a latex-enhanced turbidimetric immunoassay (L-TIA; Shima Laboratories, Tokyo, Japan), and PG I to PG II ratios (PG I/II) were calculated. Because we hypothesized that the presence of anemia and systemic inflammation would be related to the condition of the gastric mucosa, we measured the levels of hemoglobin, serum albumin, and plasma C-reactive protein (CRP).

6. Statistical analysis

All statistical analyses were performed with SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). Possible baseline covariates associated with the endoscopic diagnosis of IM were analyzed by univariate analysis with a chi-square test, linear by linear association, or a t-test. Multivariate logistic regression analysis was performed for these covariates and expressed as odds ratio (OR) and 95% confidence interval (CI). A p-value <0.05 was regarded as statistically significant.

RESULTS

1. Baseline demographic data

Table 1 shows the baseline characteristics of the enrolled patients. All 1,333 enrolled subjects were of South Korean origin.

The patients were classified into the control (n=340), DU (n=150), BGU (n=169), cancer (n=527), and dysplasia (n=147) groups. The high ratio of cancer to control was originated that the control subjects could not accept the *H. pylori* tests in the absence of gastroduodenal disease. The mean age was 57.7 years (781 male and 552 female). Patients in their 50s (24.3%) or 60s (31.3%) accounted for most of the subjects. Out of 1,333 subjects, 1,114 (83.6%) did not have IM according to endoscopic results and 219 (16.4%) had endoscopically diagnosed IM. Endoscopic IM-positive findings were significantly higher among males (p=0.040) and patients with gastroduodenal disease (p<0.001). Mean levels of serum PG II were higher in the endoscopically diagnosed IM group compared to the IM-negative group (p=0.038). However, the levels of other serologic markers were not different between the two groups. There were no significant differences of alcohol consumption, smoking, or *H. pylori* infection according to endoscopic IM results.

2. Prevalence and distribution of IM

The overall prevalence of endoscopically and histologically diagnosed IM cases were 16.4% and 59.9%, respectively. The prevalence of histological IM in the antrum (52.7%) was higher than in the body of the stomach (36.3%). When analyzed according to age (Fig. 2A), the frequency of endoscopically diagnosed IM significantly increased in proportion to age (linear by linear association, p<0.001). Similar to endoscopic IM, the prevalence of histological IM (Fig. 2B) which was found only in the antrum or in either of the stomach, significantly increased in proportion to age (linear by linear association, p<0.001). However, the prevalence of histological IM which was found only in the body did not change depending on age.

The distribution of endoscopic IM grade is shown in Table 2. Grade I was most commonly observed. All subjects with grade III showed the presence of IM histologically. The severity of endoscopic grade was closely associated with the presence of
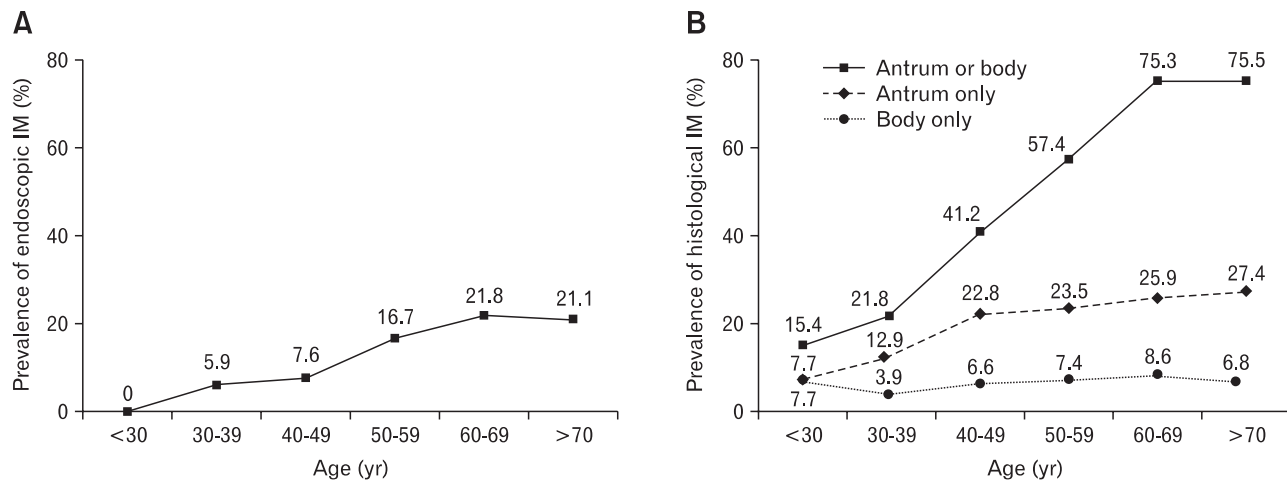

Fig. 2. The prevalence of endoscopic intestinal metaplasia (IM) (A) and histological IM (B) depending on age. Both endoscopic and histological IM increased proportionally with age (p<0.001). However, there was no significant increase in histological IM, which was found only in the body.

Table 2. The Distribution of Endoscopic Intestinal Metaplasia (IM) Grade Based on Histology of the Stomach

	Histological IM absent (n=534)	Histological IM present (n=799)	Total (n=1,333)	p-value
Endoscopic IM grade				<0.001*
Absent	497 (93.1)	617 (55.4)	1,114	
Present	37 (6.9)	182 (44.6)	219	
Grade I	29 (78.4)	134 (73.6)	163	
Grade II	8 (21.6)	43 (23.6)	51	
Grade III	0 (0)	5 (2.8)	5	

Data are presented as number (%).
*Statistical significance.

histological IM (p<0.001).

Histological evaluation showed higher grades of chronic inflammation in subjects with endoscopic IM in the body of the stomach compared to those without (p<0.038) (Table 3). In addition, the prevalence of atrophy and IM was significantly higher in the subjects with endoscopically diagnosed IM in both of the antrum and body of the stomach compared to those without (Table 3).

For IM subtyping, HID-AB2.5 staining was performed on the biopsy specimens that showed the presence of IM by H&E staining. These included specimens from the antrum of 325 cases and from the body of 238 cases. The proportions of IM subtypes I, II, and III relative to the total number of histological IM cases

Table 3. The Distribution of Gastritis and Intestinal Metaplasia (IM) Subtypes According to Endoscopic IM

	Endoscopic IM absent (n=1,114)	Endoscopic IM present (n=219)	Total (n=1,333)	p-value		Endoscopic IM absent (n=1,114)	Endoscopic IM present (n=219)	Total (n=1,333)	p-value
Inflammation activity					Body				0.001*
Antrum				0.855	Absent	707 (63.7)	112 (51.4)	819 (61.7)	
Absent	361 (32.6)	69 (31.7)	430 (32.4)		Mild	216 (19.5)	47 (21.6)	263 (19.8)	
Mild	274 (24.7)	53 (24.3)	327 (24.6)		Moderate	153 (13.8)	44 (20.2)	197 (14.8)	
Moderate	405 (36.5)	85 (39.0)	490 (36.9)		Marked	34 (3.1)	15 (6.9)	49 (3.7)	
Marked	69 (6.2)	11 (5.0)	80 (6.0)		IM				
Body				0.156	Antrum				<0.001*
Absent	328 (29.5)	55 (25.1)	383 (28.8)		Absent	579 (52.0)	51 (23.3)	630 (47.3)	
Mild	230 (20.7)	39 (17.8)	269 (20.2)		Mild	229 (20.6)	67 (30.6)	296 (22.2)	
Moderate	465 (41.9)	110 (50.2)	575 (43.2)		Moderate	228 (20.5)	76 (34.7)	304 (22.8)	
Marked	88 (7.9)	15 (6.8)	103 (7.7)		Marked	78 (7.0)	25 (11.4)	103 (7.7)	
Chronic inflammation					Body				<0.001*
Antrum				0.061	Absent	747 (67.1)	102 (46.6)	849 (63.7)	
Absent	7 (0.6)	1 (0.5)	8 (0.6)		Mild	165 (14.8)	50 (22.8)	215 (16.1)	
Mild	295 (26.6)	41 (18.8)	336 (25.4)		Moderate	148 (13.3)	52 (23.7)	200 (15.0)	
Moderate	688 (62.1)	156 (71.6)	844 (63.7)		Marked	54 (4.8)	15 (6.8)	69 (5.2)	
Marked	117 (10.6)	20 (9.2)	137 (10.3)		IM subtype				
Body				0.038*	Antrum				
Absent	3 (0.3)	0 (0)	3 (0.2)		Absent	594 (70.3)	55 (42.6)	649 (66.6)	
Mild	348 (31.3)	49 (22.4)	397 (29.8)		Present	251 (29.7)	74 (57.4)	325 (33.4)	<0.001*,† /0.389‡
Moderate	649 (58.4)	141 (64.4)	790 (59.4)		Type I	37 (14.7)	10 (13.6)	47 (14.4)	
Marked	111 (10.0)	29 (13.2)	140 (10.5)		Type II	122 (48.6)	32 (43.2)	154 (47.4)	
Atrophy					Type III	92 (36.7)	32 (43.2)	124 (38.2)	
Antrum				<0.001*	Body				
Absent	505 (45.5)	64 (29.4)	569 (42.8)		Absent	754 (80.1)	104 (67.1)	858 (78.3)	
Mild	377 (34.0)	87 (39.9)	464 (34.9)		Present	187 (19.9)	51 (32.9)	238 (21.7)	<0.001*,† /0.820‡
Moderate	180 (16.2)	58 (26.6)	238 (17.9)		Type I	52 (27.8)	16 (31.4)	68 (28.6)	
Marked	48 (4.3)	9 (4.1)	57 (4.3)		Type II	108 (57.8)	27 (52.9)	135 (56.7)	
					Type III	27 (14.4)	8 (15.7)	35 (14.7)	

Data are presented as number (%).
*Statistical significance; †Statistically significant compared with absent group; ‡Linear by linear association among the patients with histologic IM.

were 14.4%, 47.4%, and 38.2% in the antrum, and 28.6%, 56.7%, and 14.7% in the body, respectively (Table 3). The distribution of IM subtypes did not differ significantly depending on endoscopic diagnosis of IM in either the antrum (p=0.389) or body (p=0.820).

3. Detection rates of IM by endoscopy in the antrum and body

The sensitivity and specificity of endoscopic IM diagnosis were calculated based on the histological confirmation of IM. The sensitivity and specificity of endoscopic IM were found to be 24.0% (168/703) and 91.9% (579/630) in the antrum, and 24.2% (117/484) and 88.0% (747/849) in the body, respectively (Table 4). When the sensitivity and specificity of the endoscopic diagnosis of IM were calculated in the pool of control, DU, and BGU excluding neoplastic disease groups (cancer and dysplasia groups), the sensitivity and specificity were found to be 20.6% (46/223) and 92.6% (403/435) in the antrum, and 22.2% (28/126) and 90.6% (483/533) in the body, respectively (data not shown). These results were similar to the sensitivity and specificity of all patients in this study (n=1,333).

4. Identification of factors that affect the sensitivity of endoscopic IM diagnosis

To identify factors that affect the sensitivity of endoscopic diagnosis of IM in the antrum and body, univariate analysis was performed to examine the influence of age, gender, smoking, alcohol consumption, gastroduodenal diseases, *H. pylori* infection, PG I/II ratio, hemoglobin, albumin, CRP, IM subtype, endoscopic AG, mucosal inflammation activity, and chronic inflammation. The presence of endoscopic AG (p<0.001), age older than 50 years (p=0.046), and gastroduodenal diseases (p=0.042) were associated with increased endoscopic sensitivity in the antrum. Multivariate analysis showed that two factors, the presence of endoscopic AG (OR, 4.73; 95% CI, 2.07 to 10.79) and activity of mucosal inflammation (OR, 2.21; 95% CI, 1.08 to 4.54) were

associated with increased sensitivity of endoscopic diagnosis of IM in the antrum (Table 5).

Univariate analysis demonstrated that the presence of endoscopic AG (p<0.001), age older than 50 years (p=0.041), and gastroduodenal diseases (p=0.003) were associated with increased endoscopic diagnostic sensitivity of IM in the body (Table 6). Multivariate analysis showed that the presence of endoscopic AG (OR, 8.02; 95% CI, 4.55 to 14.15) and dysplasia (OR, 2.40; 95% CI, 1.07 to 5.39) were associated with increased sensitivity of endoscopic IM diagnosis in the body. On the other hand, the presence of BGU (OR, 0.35; 95% CI, 0.15 to 0.081) was associated with decreased sensitivity (Table 6).

DISCUSSION

In the present study, the sensitivity and specificity of endoscopically diagnosed cases of IM that were confirmed by histology were found to be 24.0% and 91.9% for the antrum, and 24.2% and 88.0% for the body of the stomach, respectively.[19,20] The sensitivity and specificity of endoscopic AG diagnoses were found to be 61.5% and 57.7% for the antrum, and 46.8% and 76.4% for the body of the stomach in the same cohort of the present study.[23] The low concordance rate of IM is rather disappointing. However, results of the present study showing that all patients with IM severity grade I by white light endoscopy (WLE) was difficult to be diagnosed without confirmation by histology. This suggests that a high index of suspicion for endoscopic diagnosis of gastric IM is important, especially when the grade of endoscopic IM is minor. As the frequency of histological IM significantly increased in proportion to age in the present study, high index of suspicion of IM could be important in old age.

There were a few studies which specific IM subtype such as incomplete type was related with increased risk of gastric cancer.[5,12,24] But the present study showed that the severity of IM subtypes was not related to an endoscopic diagnosis of IM. This

Table 4. The Sensitivity, Specificity, PPV, NPV, and Diagnostic Accuracy of Endoscopic IM Based on Histological IM

	Endoscopic IM absent	Endoscopic IM present	Total	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Diagnostic accuracy, %
Antrum								
Histological IM absent	579	51	630	24.0	91.9	76.7	52.0	56.0
Histological IM present	535	168	703					
Body								
Histological IM absent	747	102	849	24.2	88.0	53.4	67.1	64.8
Histological IM present	367	117	484					
Total								
Histological IM absent	497	37	534	22.8	93.1	83.1	44.6	50.9
Histological IM present	617	182	799					

PPV, positive predictive value; NPV, negative predictive value; IM, intestinal metaplasia.

Table 5. The Univariate and Multivariate Analyses for the Factors Affecting the Sensitivity of the Endoscopic Diagnosis of IM in 703 Subjects with Histological IM in the Antrum

	Endoscopic IM absent (n=535)	Endoscopic IM present (n=168)	Total	Univariate p-value	Multivariate p-value	OR (95% CI)
Endoscopic AG						
Absent	201 (92.2)	17 (7.8)	218			1.0
Present	334 (68.9)	151 (31.1)	485	<0.001*	<0.001*	4.73 (2.07-10.79)*
Inflammation activity						
Absent	158 (74.5)	54 (25.5)	212			1.0
Present	375 (76.8)	113 (23.2)	488	0.509	0.030*	2.21 (1.08-4.54)*
Chronic inflammation						
Absent	3 (75.0)	1 (25.0)	4			
Present	528 (76.1)	166 (23.9)	694	0.960		
Age, yr						
<50	84 (84.0)	16 (16.0)	100			1.0
≥50	451 (74.8)	152 (25.2)	603	0.046*	0.786	0.88 (0.36-2.13)
Gender						
Male	357 (75.8)	114 (24.2)	471			1.0
Female	178 (76.2)	54 (23.3)	232	0.786	0.371	0.74 (0.38-1.42)
Smoking						
No	200 (77.2)	59 (22.8)	259			
Yes	326 (75.1)	108 (24.9)	434	0.531		
Alcohol						
No	162 (74.0)	57 (26.0)	219			
Yes	362 (76.9)	109 (23.1)	471	0.409		
Disease				0.042*		
Control	78 (75.0)	26 (25.0)	104			1.0
DU	37 (90.2)	4 (9.8)	41		0.313	0.46 (0.10-2.06)
BGU	62 (79.5)	16 (20.5)	78		0.121	0.44 (0.15-1.24)
Cancer	279 (76.9)	84 (23.1)	363		0.141	0.54 (0.24-1.22)
Dysplasia	79 (67.5)	38 (32.5)	117		0.737	1.19 (0.42-3.35)
H. pylori infection						
Negative	56 (69.1)	25 (30.9)	81			1.0
Positive	479 (77.0)	143 (23.0)	622	0.118	0.096	0.46 (0.18-1.14)
PG I/II ratio						
<3	235 (76.8)	71 (23.2)	306			1.0
≥3	239 (77.9)	68 (22.1)	307	0.756	0.253	1.41 (0.78-2.57)

Data are presented as number (%).
IM, intestinal metaplasia; OR, odds ratio; CI, confidence interval; AG, atrophic gastritis; DU, duodenal ulcer; BGU, benign gastric ulcer; *H. pylori*, *Helicobacter pylori*; PG, pepsinogen.
*Statistical significance.

result was not so different from the findings of a previous study showing that IM subtype does not play a major role in predicting gastric cancer development.[8] In addition, CDX2 expression, which plays an important role in the formation of IM, increases according to histological grade of IM but is not associated with IM subtype.[25] Taken together, IM subtype is not likely to be useful for endoscopically diagnosing IM. Instead, histological IM

grade appears to be more important for diagnosing this disease.

Since the sensitivity of endoscopic-based diagnoses of IM was low in the present study, we analyzed factors that may affect this sensitivity. Our study showed that the presence of endoscopic finding of AG was associated with increased sensitivity of endoscopic-based diagnosis of IM in both the antrum and body. These results correspond with those of earlier studies

Table 6. The Univariate and Multivariate Analyses for the Factors Affecting the Sensitivity of the Endoscopic Diagnosis of IM in 484 Subjects with Histological IM in the Body

	Endoscopic IM absent (n=367)	Endoscopic IM present (n=117)	Total	Univariate p-value	Multivariate p-value	OR (95% CI)
Endoscopic AG						
Absent	107 (89.9)	12 (10.1)	119			1.0
Present	260 (71.2)	105 (28.8)	365	<0.001*	<0.001*	8.02 (4.55-14.15)*
Inflammation activity						
Absent	66 (75.0)	22 (25.0)	88			1.0
Present	298 (75.8)	95 (24.2)	393	0.870	0.723	0.90 (0.53-1.53)
Chronic inflammation						
Absent	0 (0)	0 (0)	0			
Present	365 (75.7)	117 (24.3)	482			
Age, yr						
<50	47 (87.0)	7 (13.0)	54			1.0
≥50	320 (74.4)	110 (25.6)	430	0.041*	0.066	1.73 (0.96-3.12)
Gender						
Male	259 (76.0)	82 (24.0)	341			1.0
Female	108 (75.5)	35 (24.5)	143	0.920	0.388	0.80 (0.49-1.31)
Smoking						
No	130 (75.6)	42 (24.4)	172			
Yes	230 (75.7)	74 (24.3)	304	0.985		
Alcohol						
No	116 (74.8)	39 (25.2)	155			
Yes	241 (76.0)	76 (24.0)	317	0.778		
Disease					0.003	
Control	58 (75.3)	19 (24.7)	77			1.0
DU	3 (100.0)	0 (0.0)	3		0.754	0.88 (0.40-1.94)
BGU	37 (80.4)	9 (19.6)	46		0.015*	0.35 (0.15-0.81)*
Cancer	200 (76.9)	60 (23.1)	260		0.465	0.80 (0.44-1.44)
Dysplasia	69 (70.4)	29 (29.6)	98		0.033*	2.40 (1.07-5.39)*
H. pylori infection						
Negative	45 (73.8)	16 (26.2)	61			
Positive	322 (76.1)	101 (23.9)	423	0.688	0.876	0.94 (0.48-1.85)
PG I/II ratio						
<3	207 (77.5)	60 (22.5)	267			
≥3	115 (77.2)	34 (22.8)	149	0.935		

Data are presented as number (%).

IM, intestinal metaplasia; OR, odds ratio; CI, confidence interval; AG, atrophic gastritis; DU, duodenal ulcer; BGU, benign gastric ulcer; *H. pylori*, *Helicobacter pylori*; PG, pepsinogen.

*Statistical significance.

which reported that IM is found more frequently in patients with AG.[26] This might be related to the fact that the degree of IM becomes more severe with atrophy as patients become older. In addition, endoscopists may be more alert to atrophy-related lesions such as IM or neoplastic disease if AG is found by endoscopy.

It is generally accepted that intestinal-type gastric adenocarcinoma arises through a multistep process that progresses from gastritis through stages characterized by atrophy, IM, dysplasia, and finally intestinal-type cancer.[1] In the present study, the presence of dysplasia was actually related to increased sensitivity of endoscopic-based diagnosis of IM in the body. However, the presence of gastric cancer itself was not related to this sensitivity in either the antrum or body. This result might be due to

the fact that gastric cancer includes not only intestinal-type but also diffuse-type adenocarcinomas according to Lauren classification. In South Korea, the percentage of diffuse-type gastric cancer which is usually not associated with IM is rather high (42.1%) so that the influence of gastric cancer for the sensitivity of IM could be lower than that of dysplasia.[27]

Interestingly, activity of mucosal inflammation in the antrum was significantly related to increased sensitivity of endoscopic diagnosis of IM. As nodular mucosal changes are the most important finding for the conventional endoscopic diagnosis of IM, the active mucosal inflammation could contribute to mucosal nodulation through neutrophil infiltration. In contrast, a previous study found that elevated CRP level (>5 mg/dL) was associated with decreased sensitivity of endoscopic diagnosis of AG in the body.[23] This could be explained by decreased transparency of submucosal vessel caused by neutrophil infiltration. In addition, the presence of BGU was related to decreased sensitivity of endoscopic IM diagnosis in the body. Taken together, our findings indicated that localized or systemic inflammation could affect the sensitivity of endoscopic diagnosis by influencing the condition of the gastric mucosa, and the affecting factors might be different for the endoscopic diagnoses of AG and IM.

There have been many attempts to establish an accurate method for detecting IM. For instance, the term 'special type intestinal metaplasia' was coined in a Japanese study to describe ash-colored nodular changes of the mucosa.[28] Another study attempted to use a chromoendoscopic method with methylene blue to diagnose IM.[29] In addition, a new system for endoscopic classification of chronic gastritis has been developed based on histology.[19] IM was also defined as a lesion appearing as ash-colored nodular changes, but the sensitivity and specificity of this diagnostic procedure were found to be 6% to 12% and 98% to 99%, respectively. It was finally concluded in this study that ordinary endoscopic examination techniques are unsuitable for diagnosing intestinal metaplastic gastritis.[19] A similar trial was performed in a Romanian study, in which IM was detected as nodular gray mucosa along with methylene blue chromoendoscopy.[20] The sensitivity and specificity were 6.1% and 99.5%, respectively.[20] In contrast, a Taiwanese study found that overall sensitivity and specificity were 75% and 68.1% when using a similar endoscopic criteria such as that the presence of whitish plaques, patches, or homogeneous whitish discoloration on the gastric mucosa.[18] These results suggest that significant discrepancies exist among different studies even when conventional endoscopic criteria such as mucosal color changes and nodulation are used for detecting gastric IM. Consequently, a high index of suspicion is important for detecting gastric IM especially when dealing with cases of flat or depressed types of IM.[30]

Conventional WLE is associated with a number of limitations; thus, narrow band imaging (NBI) and magnifying endoscopy (ME) could be promising techniques for increasing the diagnostic accuracy of precancerous lesions.[31,32] One study used NBI for targeted biopsy and surveillance of gastric IM and reported that the sensitivity and specificity of first/second surveillances are 78.8%/91.3% and 82.5%/89.1%, respectively.[33] Similarly, another study reported that NBI increases the diagnostic yield for the detection of IM and dysplasia, and showed that the sensitivity and specificity of NBI were 71% and 58%, respectively.[34] However, examining the whole stomach by NBI and ME may be difficult and time-consuming. Thus, precise and close examination by WLE should be initially performed; NBI and ME could be used for further evaluation of specific lesion identified by WLE. Therefore, if endoscopic criteria for easy and quick detection of IM are established, the endoscopic detection rate of IM would be increased with the combined use of NBI and ME.

In conclusion, this study showed that the endoscopic diagnosis of IM by conventional WLE was rather disappointing. Thus, a high index of suspicion is important for increasing the sensitivity of endoscopic diagnoses of IM, especially when endoscopic AG is absent, and confirmation of the diagnosis by histology is necessary.

CONFLICS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

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