Conflict of interest: The authors have no conflict of interest to disclose.

Ethical Statement: This study was approved without the need for individual informed consent by our institutional ethics committee and is in accordance with the 1964 Declaration of Helsinki and its later amendments.

Original Article
Abstract

 PURPOSE: To investigate the correlation between ABC risk assessment and radiological findings of gastric mucosa and to propose an improved method for gastric cancer screening.

 MATERIALS AND METHODS: We evaluated 318 participants with Helicobacter pylori (Hp) antibody titers, serum pepsinogen (PG) and upper GI radiography and then classified them into 3 groups: A, double-negative; B, Hp-positive, PG-negative; and C, PG-positive. Group A was subclassified as: A-1, Hp antibody titer <3.0 U/mL; and A-2, Hp antibody titer ≥3.0 U/mL. Results for Group A and non-A (B or C) participants and radiological findings of gastric mucosa (fold and area gastricae) were analyzed retrospectively.

 RESULTS: Radiological findings differed significantly between the 207 A-1 and 98 non-A group. Odds ratios were 17.72 for fold distribution, 10.63 for fold thickness, 6.10 for fold characteristics, and 10.62 for area gastricae. Presence of ≥2 risk factors offered 90.3% sensitivity, 94.7% specificity, and 93.3% accuracy. Nine (69.2%) of the 13 A-2 group participants and 11 (5.3%) A-1 group participants had a risk for gastric cancer according to radiological findings.

 CONCLUSION: A good correlation exists between ABC classifications and radiological findings for gastric cancer risk, but some discrepant cases exist. We recommend both methods as screening for gastric cancer.

 KEY WORDS: Helicobacter pylori; ABC classification; gastric cancer; radiological finding
1. Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death in both sexes worldwide. The highest estimated mortality rates are in Eastern Asia, particularly in China, Korea, and Japan [1]. About 50,000 individuals die every year from gastric cancer in Japan, so mass screening is considered important. Among the methods of screening for gastric cancer used in Japan, upper GI radiography appears effective in reducing mortality rates and is recommended for population-based and opportunistic screening until 2014 [2-4]. Meanwhile, the ABC classification with stratification for gastric cancer risk is also seeing increasing use [5-7].

The ABC risk classification is based on Helicobacter pylori (Hp) infection and atrophic changes as two factors associated with the development of gastric cancer. Hp antibodies (antigen) and serum pepsinogen (PG) levels are measured, then screened individuals are classified into 3 groups based on the results: A, Hp-negative and PG-negative; B, Hp-positive and PG-negative; or C, PG-positive (Table. 1).

The detection rate for gastric cancer is highest in the order of Group C, B, and A, and screening intervals are based on this risk assessment. As secondary screening, instead of upper gastrointestinal (GI) radiography, upper GI endoscopy is regularly performed to achieve a higher rate of early detection. An ABCD classification can also be used, with Group C patients showing low or negative Hp antibody titers classified as Group D.

The ABC classification for gastric cancer risk has mainly been adopted for occupational medical
screening, but several problems have been identified. The most important is that, although gastric cancer is thought to develop rarely in Group A, gastric cancer still occurs in some Group A patients based on the ABC risk classification. In fact, when ABC risk assessment is used together with upper GI radiography, some patients classified as Group A show radiological findings similar to Group B or C. The reason for this may be a problem in the cut-off values that have been established for these laboratory tests [8].

The purpose of this study was to thus investigate correlations between ABC risk assessment and radiological findings of background mucosa and to propose the practical application of those findings in gastric cancer screening.

2. Materials and Methods

This study included 318 participants (134 men, 184 women) in an occupational medical screening program who were evaluated using the ABC classification and upper GI radiography on the same day. Mean age was 46.8 years (range, 30-70 years; median, 46 years). Patients with a history of Hp eradication therapy or for whom radiological images were of poor quality were excluded.

The ABC classification is based on serum measurement of Hp antibodies and pepsinogen (PG) levels. HP antibody titers and PG levels were measured using commercial kits for Hp antibodies (E-Plate Eiken H. pylori antibody; Eiken Chemical, Tokyo, Japan) and PG (LZ-Test Eiken pepsinogen I and II; Eiken Chemical). The cut-off value for Hp antibody titers was 10.0 U/mL, and the cut-off value for PG was PG
I \leq 70.0 \text{ ng/mL} \text{ and } \text{PG I/II ratio} \leq 3.0.

Participants were classified into 3 groups: A, Hp-negative and PG-negative; B, Hp-positive and PG-negative; or and C, PG-positive. There were 220 participants in Group A, 48 in Group B, and 50 in Group C. Group A is usually defined as Hp-negative and PG-negative, but some studies have reported that Hp antibody titers of 3.0 U/mL to <10.0 U/mL may be seen with previous Hp infection [8]; therefore, Group A was further subclassified, based on Hp antibody titers, into Group A-1 (<3.0 U/mL) and Group A-2 (3.0 to <10.0 U/mL). There were 207 participants in Group A-1 and 13 in Group A-2. Group A-1 was defined as a low-risk group for gastric cancer, and the non-A groups (B or C) were defined as a high-risk group.

Upper GI radiography was performed using barium contrast (Barytester A240 powder; 240-w/v% 150 ml; Fushimi Pharmaceutical, Marugame, Japan) and a gas-forming agent (Baryace 5.0 g; Fushimi Pharmaceutical). Radiography was performed using a digital radiographic system with a flat panel detector (radiographic equipment: SONIALVISION Safire II; SHIMADZU Corporation, Kyoto, Japan), in accordance with the imaging guidelines of the Japanese Society of Gastrointestinal Cancer Screening. Radiological findings that were evaluated included gastric folds and the area gastricae. Fold distribution, thickness, and characteristics were assessed using a monochrome monitor (Radiforse GX340, 3 megapixels; EIZO Corporation, Hakusan, Japan).

Fold distribution area was evaluated on a frontal view on double-contrast radiography in a supine
position (angular incisure as a reference). The gastric corpus was divided crosswise into 4 equal zones, and the number of zones where folds were present was recorded (Fig. 1). Fold thickness was evaluated on a frontal or right anterior oblique (RAO) view on double-contrast radiography in a supine position, with measurement of the maximum transverse diameter of prominent folds. Fold characteristics were classified into 3 categories based on fold margins: regular; intermediate; or irregular (Fig. 2). The area gastricae (mucosal pattern) in two areas, the gastric antrum and gastric corpus, was classified into 3 categories: smooth; intermediate; and coarse (Fig. 3). Fold characteristics and area gastricae were assessed based on the prior literature as a reference [9,10].

Radiographs were interpreted according to consensus decisions by two radiologists, both certified by the Japan Radiological Society. The radiologists were blinded to ABC classification results when interpreting radiographs.

The correlation between each radiological finding and the ABC classification was retrospectively analyzed based on the results. This included: 1) the correlation between ABC classification (serum risk assessment) with each radiologic finding in the low-risk (A-1) and high-risk groups (non-A = B or C groups); and 2) the correlation with each radiologic finding only in Group A. Analysis included a comparison between Groups A-1 and A-2, and within Group A-1, discrepancies were seen between ABC classification results and radiological findings. Between-group differences in fold distribution and fold thickness were examined by the Mann-Whitney test. Differences in fold characteristics and area gastricae
were examined using the Cochran-Armitage test. In statistical analyses, values of $p < 0.05$ were considered to indicate significant difference.

Based on the results, correlations between radiological findings and risk assessment were examined, with the non-A groups defined as high-risk. Multivariate analysis was performed using ABC classification results as a reference. Risk factors were defined as fold distribution in ≤2 zones, fold thickness ≥3.9 mm, irregular fold characteristics, and coarse area gastricae (mucosal pattern) in either the gastric corpus or antrum. As evidence of risk factors, cut-off values for fold distribution and fold thickness were calculated from receiver operating characteristic (ROC) curves.

3. Results

1) Correlation between radiological findings and ABC classification of gastric cancer risk

Fold distribution was zero in 5 non-A group participants. These participants were excluded from the evaluation of fold thickness and fold characteristics and from multivariate analysis. All 5 of these participants were in Group C.

Fold distribution based on the 4-divided zones of the gastric corpus was: Group A (A-1 group), 3.60 ± 0.65 zones; and non-A groups, 2.10 ± 0.94 zones. Fold thickness was: Group A, 2.94 ± 0.64 mm; and non-A groups, 4.62 ± 1.30 mm. Both findings differed significantly between groups.

Fold characteristics in Group A were: regular in 169 (81.6%), intermediate in 32 (15.5%), and
irregular in 6 (2.9%) participants; and in the non-A groups they were: regular in 9 (9.7%), intermediate in 27 (29.0%), and irregular in 57 (61.3%) participants. The area gastricae (mucosal pattern) for the gastric antrum in Group A was: smooth in 178 (86.0%), intermediate in 2 (1.0%), and coarse in 27 (13.0%) participants; for the gastric corpus, it was: smooth in 188 (88.4%), intermediate in 1 (0.5%), and coarse in 18 (8.7%) participants. The area gastricae (mucosal pattern) for the gastric antrum in the non-A groups was: smooth in 7 (7.1%), intermediate in 6 (6.1%), and coarse in 85 (86.7%) participants; for the gastric corpus, it was: smooth in 13 (13.3%), intermediate in 11 (11.2%), and coarse in 74 (75.5%) participants (Table 2, Fig. 4).

Area under the curve (AUC) on ROC was 0.89 for fold distribution and 0.90 for fold thickness. Odds ratios for each parameter (95% confidence interval (CI)) were: fold distribution, 17.72 (6.10-51.45); fold thickness, 10.63 (3.68-30.66); fold characteristics, 6.10 (1.71-21.73); and area gastricae, 10.62 (3.80-29.68). Risk assessment based on any 2 of these factors being positive offered 90.3% sensitivity, 94.7% specificity, 93.3% accuracy, 88.4% positive predictive value (PPV), and 95.6% negative predictive value (NPV) (Table 3).

When the relationship between fold distribution and PG I/II ratio was examined, mean PG I/II ratio according to the number of zones was: 4 zones, 5.2; 3 zones, 4.6; 2 zones, 3.4; 1 zone, 2.6; and 0 zones, 1.2. Thus, as the number of zones where gastric folds were present decreased, PG I/II ratio also tended to decrease.
2) Radiological findings in the low-risk group (Group A) for gastric cancer

In Group A-2, mean fold distribution was 2.31 ± 1.03 zones, and fold thickness was 4.36 ± 1.40 mm. Fold distribution and fold thickness both differed significantly between Group A-2 and Group A-1. In Group A-2, fold characteristics were regular in 3 participants (23.1%), intermediate in 4 (30.8%), and irregular in 6 (46.2%). Area gastricae (mucosal pattern) in both the gastric antrum and corpus was smooth in 5 participants (38.5%), intermediate in 3 (23.1%), and coarse in 5 (38.5%). Nine (69.2%) of the 13 Group A-2 participants had ≥2 risk factors (Table 4, Fig. 5). Among the 207 Group A-1 participants, 11 (5.3%) had ≥2 radiological risk factors (Table 5).

4. Discussion

Hp infection is associated with the development of gastric cancer [11,12], and interest has focused on Hp testing as screening for gastric cancer. The ABC risk classification is a method of determining the risk of gastric cancer by combining the assay for Hp infection with the results of PG measurement as a reflection of the degree of atrophy. Prospective studies have reported meaningful results with this method [5-7], which is primarily being used in occupational medical screening in Japan, but low detailed examination rates and the difficulty of follow-up evaluation are cited as important problems. One problem often identified is that some Group A patients, regarded as having the lowest risk for gastric cancer, still
appear to be at high risk based on imaging studies. Prospective studies have reported gastric cancer developing in Group A patients [13-15].

The ABC risk classification assumes that patients with a history of Hp eradication therapy are excluded from testing. However, one drawback is reliance on the memory of the individuals being screened. In addition, some patients have unintentionally undergone Hp eradication when taking antibiotics for another type of infection. Excluding a patient from testing based on medical history is impossible in such cases. Furthermore, gastric cancer cannot be detected based on ABC risk classification alone, and patients must be reminded that follow-up evaluation is important.

On the other hand, upper GI radiography is often reported to be useful in diagnosing Hp infection and evaluating the degree of atrophy [9,10,16-21]. By introducing Hp infection and atrophy evaluation on conventional upper GI radiography as a new diagnostic criterion, the concepts of gastric cancer screening and ABC risk classification can be implemented together [22]. The few reports to date of a relationship between ABC classification and gastric radiological findings have been from Japan [10, 20, 23]. The present study showed a high correlation with risk assessment based on radiological findings of fold distribution, fold thickness, fold characteristics, and area gastricae used as indices. Moreover, fold distribution correlated with PG I/II ratio, which reflected the degree of gastric atrophy. If a positive result for any two of these four factors in the gastric radiological findings is taken as an index for determining risk, the correct diagnosis rate is 93.3%; this therefore appears to be a method for determining risk that
would be sufficiently robust for practical use. All four cited factors have been evaluated in prior studies and various criteria for risk determination have been established, but with folds in particular it should be borne in mind that fold thickness, characteristics, and distribution all vary according to the quantity of gas-forming agent used. The impression of fold characteristics varies according to the amount of air and the body position, and many cases in the present study were judged to be intermediate. The fold thickness that serves as an index of H. pylori infection varies greatly between researchers, from 4.5 mm, when 3.5 g of gas-inducing agent was administered prior to the screening test [9], to 3 mm, when 6 g of agent was administered [10]. We performed screening tests with 5 g of gas-inducing agent, in accordance with the guidelines for imaging methods of the Japanese Society of Gastrointestinal Cancer Screening, and the cut-off value was 3.9 mm. With regard to fold distribution, one study did not take this into consideration as a factor for determining gastric cancer risk [20], and another maintains that it should not be taken into consideration at all [21]. At the same time, one study maintains that determination of risk by fold distribution is valid [9], and yet another considers fold distribution as superior to the PG method for determining degree of atrophy [24]. The present study found a relationship between the range of fold distribution and PGI/II ratio, representing a reflection of the degree of atrophy. The evaluation method that we devised using double-contrast radiography in a supine position with the gastric corpus divided into four zones allows numerical expression of the extent of fold distribution, and is thus simpler and offers greater objectivity than previously reported classifications.
In this study, 98 (30.8%) among the 318 subjects were judged to be at risk of gastric cancer (non-A group) according to ABC classification. All 318 subjects were analyzed retrospectively purely based on radiological findings, and an additional 20 patients were classified as non-A group, bringing the total to 118 (37.1%). Nine of 13 patients (69.2%) in Group A-2 were positive for two risk factors, thus showing some discrepancy with the ABC risk classification. On retrospective reexamination of these data in light of risk assessment results, no changes in diagnoses were made. These findings are in agreement with previous reports. Therefore, this Group A-2 should not be treated as a low-risk group based on ABC classification alone, and upper GI radiography should also be performed. Among the 207 participants in Group A-1, 11 (5.3%) were positive for ≥2 radiological risk factors. On retrospective review, 3 of the 4 participants with fold distribution as a positive risk (0-2 zones) showed hyperextension. In 3 of the 4 participants with irregular fold characteristics, the reason was insufficient air volume. In 5 of the 10 participants with coarse area gastricae, the gastric mucosa without atrophy showed reticular changes. By limiting the 4 factors to positive risk for fold distribution without hyperextension, irregular fold characteristics, fold thickness ≥3.9 mm, and coarse area gastricae (excluding normal reticular changes), re-evaluation showed that 5 participants (2.4%) actually had ≥2 factors (Table 5). Careful attention must therefore be paid to fold changes due to air volume and small area gastricae with a reticular pattern that may be considered normal. In previous reports about imaging evaluation in Group A-1, atrophic changes were indicated by radiological findings in 204 of 4504 cases (4.5%) [20] and by endoscopic findings in
32 of 506 cases (6.3%) [25]. In view of the foregoing, at the very least it is dangerous to treat Group A-2 as a low-risk group from the ABC risk classification, and because Group A-1 also includes a certain number of participants in the risk group from the gastric radiological examination, classification into Group A should be evaluated together with interpretation of gastric radiographs.

While the present study was evaluated using a digital direct radiographic system in occupational medical screening for gastric cancer, analog indirect radiographic systems are generally used in population-based gastric cancer screening. The latter shows some area of inferiority such as small film size, and difficulty in measuring and zooming-in on findings. However, apparent fold thickening and marginal irregularity, and coarse area gastricae are easily detected using analog indirect radiographic systems, and no differences are apparent in the evaluation of fold distribution, regardless of radiographic system. We therefore believe a risk-assessment method based on the present study will be able to be applied to population-based gastric cancer screening using indirect radiographic systems.

A number of limitations to the present study should be considered. The first is that the determination of Hp infection was made only by Hp antibody titer carried out in an occupational medical screening program, whereas it is generally considered desirable to determine Hp infection on the basis of multiple methods of testing. Next, among the findings from radiological imaging using barium that are taken as risk factors, fold characteristics are particularly susceptible to the subjectivity of the person interpreting the radiograms, and many cases were judged to be intermediate. Also, it should be borne in mind that fold
distribution varies with the volume of gas, and several cases were underestimated due to hyperextension.

Finally, as there are no pathological grounds for risk evaluation by image diagnosis, it would naturally be desirable for all cases to undergo pathological evaluation by endoscopy and biopsy. From the above, the cutoff point for Hp infection should ideally be determined by multiple testing methods, and there is scope for reexamination of the methods for evaluating folds from radiological findings; also, studies should be performed with a greater number of cases once pathological grounds for evaluation of risk from images have been obtained. This study was conducted within the bounds of a pragmatic method for health screening with these limitations.

5. Conclusion

ABC classification for gastric cancer risk assessment is a good base, but it has some problems and can be improved. Upper GI radiography might be able to detect the small percentage of high risk patients classified in the ABC low risk group. On initial gastric cancer screening, both upper GI radiography and ABC classification should be performed, and these may complement each other in the risk assessment of gastric cancer.
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Figure Legends

Fig 1 Four divided zones of the gastric corpus

On frontal view with double-contrast radiography in a supine position (angular incisure as a reference), a cross is drawn, with the center of the gastric corpus as seen on double-contrast radiography as a reference, to divide the gastric corpus into 4 zones and assess the number of zones where folds are present. Figure 1a shows fold distribution in 4 zones in a Group A participant, and Figure 1b shows fold distribution in only one zone in a non-A group participant.

Figure 2 Fold characteristics

Fold margins are examined and classified as regular (smooth) (a); irregular with prominent bends and unevenness (c), or intermediate with in-between findings (b).

Figure 3 Area gastricae

The area gastricae is examined and classified as smooth with good imaging if the contour could not be recognized (a), coarse if the contour of the area gastricae is clearly recognized (c), and as intermediate with in-between findings (b).
**Figure 4** Non-Group A patient

A 48-year-old man: fold distribution, 2 zones; fold thickness, 5.5 mm; folds, irregular in appearance; and area gastricae, coarse. This patient is in a non-A group (Group C) based on serum assessment (ABC) with an Hp antibody titer of 77.5 U/mL and PG-positive. A good correlation exists with the radiological findings.

**Figure 5** Subtype of a Group A (A-2) patient

A 40-year-old man: fold distribution, 1 zone; fold thickness, 3.8 mm; fold appearance, irregular; and area gastricae, coarse. The patient is positive for 3 risk factors. This patient is in Group A, based on serum assessment (ABC), with an Hp antibody titer of 3.2 U/mL and PG-negative. However, a discrepancy with the radiological findings exists. With an Hp antibody titer $\geq 3.0$ U/mL, this patient is now classified in Group A-2.