Analysis of ABC (D) stratification for screening patients with gastric cancer

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Abstract

AIM: To evaluate the value of ABC (D) stratification [combination of serum pepsinogen and Helicobacter pylori (H. pylori) antibody] of patients with gastric cancer.

METHODS: Ninety-five consecutive patients with gastric cancer were enrolled into the study. The serum pepsinogen I (PG I)/pepsinogen II (PG II) and H. pylori antibody levels were measured. Patients were classified into five groups of ABC (D) stratification according to their serological status. Endoscopic findings of atrophic gastritis and histological differentiation were also analyzed in relation to the ABC (D) stratification.

RESULTS: The mean patient age was (67.9 ± 8.9) years. Three patients (3.2%) were classified into group A, 7 patients (7.4%) into group A’, 27 patients (28.4%) into group B, 54 patients (56.8%) into group C, and 4 patients (4.2%) into group D, respectively. There were only three cases in group A when the patients taking acid proton pump inhibitors and those who had undergone eradication therapy for H. pylori (group A’) were excluded. These three cases had mucosal atrophy in the grey zone according to the diagnostic manual of ABC (D) stratification. Histologically, the mean age of the patients with well differentiated adenocarcinoma was significantly higher than that of the patients with poorly differentiated adenocarcinoma (P < 0.05). There were no differences in the pattern of atrophy in the endoscopies between the well differentiated and poorly differentiated groups.

CONCLUSION: ABC (D) stratification is a good method for screening patients with gastric cancers. Endoscopy is needed for grey zone cases to check the extent of mucosal atrophy.

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Key words: Gastric cancer; Helicobacter pylori; Pepsinogen; ABC (D) stratification; Cancer screening

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INTRODUCTION

Gastric cancer remains the second leading cause of can-
Gastric cancer screening with ABC (D) stratification

November 21, 2011

Kudo T et al. Gastric cancer screening with ABC (D) stratification

H. pylori
moendoscopy with indigo carmine and a biopsy were performed. All cases were histologically confirmed to have gastric cancer. According to the endoscopic gastric mucosal findings, the patients were classified into three categories: those without atrophy, those with close-type atrophy, and those with open-type atrophy.

**Materials and Methods**

Patients and study design

Ninety-five consecutive patients with gastric cancer were enrolled in the study. All patients were diagnosed as having gastric cancer at Shirakawa Clinic (Maebashi, Japan) between November 2007 and October 2009. The mean age of the patients was (67.9 ± 8.9) years (range, 38-83, median 69). There were 72 male and 23 females. According to ABC (D) stratification, there were 3 (3.2%) patients in group A, 7 patients (7.4%) in group A', 27 (28.4%) in group B, 54 (56.8%) in group C, and 4 (4.2%) in group D, respectively (Table 1). There were no significant differences in the mean age, sex ratio, location of the tumor, macroscopic findings or histological type among the five groups. According to endoscopic findings, two cases (2.1%) had no atrophy, 21 (22.1%) had closed-type atrophy, and 72 (75.8%) had open-type atrophy. The relationship between ABC (D) stratification and the endoscopic atrophic border are shown in Table 2. There were no significant differences in the endoscopic atrophic border pattern among the five groups. There were 35 patients with closed-type or open-type atrophy in the PG negative group.

Representative cases in each group

Figure 1 shows the representative cases of gastric cancer...
in groups A-D. Figure 1A shows a 70-year-old male with *H. pylori* (-) and PG (-). However, open-type atrophy was found in endoscopy. He should have been classified into group D because of the extent of mucosal atrophy. The PG I level was low (28.5 ng/mL), although PG was negative based on the PG I /PG II ratio (3.9). Figure 1A shows a 46-year-old female with *H. pylori* (-) and PG (-). She had no atrophy in the endoscopic findings. This case received post-eradiation therapy for *H. pylori*. The patient was *H. pylori* negative with the titer of the *H. pylori* antibody under 10 U/mL. However, the antibody titer was 7.6 U/mL, so she was not completely *H. pylori* negative. Figure 1B shows a 72-year-old male with *H. pylori* (+) and PG (-). He had closed-type atrophy in the endoscopic findings. Figure 1C shows a 71-year-old male with *H. pylori* (+) and PG (+). This case was positive for both *H. pylori* and PG. He had open-type atrophy in the endoscopic examinations. Figure 1D presents a 69-year-old male with *H. pylori* (-) and PG (+). He had open-type atrophy in endoscopy. Because of the progression of mucosal atrophy, we concluded that this patient was likely negative for *H. pylori* because the organism cannot live in the atrophic mucosa.

**Gastric cancers arising from group A and group A’**

A summary of the patients with gastric cancer arising from group A and group A’ is shown in Table 3. Among 10 patients, there was one case without atrophy, 3 cases of closed-type atrophy, and 6 cases of open-type atrophy. There were only 3 (3.2%) cases in group A when the patients in group A’ (who was taking acid proton pump inhibitors and/or had received eradication therapy for *H. pylori*) were excluded. These 3 cases had mucosal atrophy and were classified into the grey zone pattern based on the diagnostic manual of *ABC (D)* stratification. Eight of the 10 patients were classified into group A or A’ because their serum PG I /PG II ratio was greater than 3. The serum PG I levels of the 8 patients were ≤ 70 ng/mL.

**Histological analysis**

Histologically, there were 76 (80.0%) cases of well or moderately differentiated adenocarcinomas (well differentiated group) (Table 4). There were 19 (20.0%) cases of poorly differentiated adenocarcinomas or signet ring cell carcinomas (poorly differentiated group). The mean age of the patients in the well differentiated group [70.2 ± 5.8 years] was significantly higher than that of the poorly differentiated group [61.4 ± 12.9 years], *P* < 0.05. There were no differences in the sex ratio or the pattern of atrophy in endoscopy between the well differentiated group and the poorly differentiated group. The proportion of group C patients tended to be higher in the well differentiated group, although it did not reach statistical significance. It was supposed that the patients with well differentiated adenocarcinomas would shift from group B to C as they aged.

The relationship between *ABC (D)* stratification and the endoscopic atrophic border according to the histological differentiation is shown in Tables 5 and 6. There were no differences in the distribution of the endoscopic atrophic border between the well differentiated and poorly differentiated groups.

**DISCUSSION**

A screening program with an upper gastrointestinal series has been confirmed to be effective for reducing mortality from gastric cancer in Japan[2,3]. Since the X-ray with photofluorography was first introduced in the 1960s, it has played a key role in gastric cancer screening[11,12]. However, the existing program by the X-ray was introduced prior to the discovery of *H. pylori* and documentation of its carcinogenicity. Only approximately 13% of the target population participated in the program[13]. Given these drawbacks, it is necessary to establish an effective screening system, focusing on high-risk status such as *H. pylori* infection and atrophic gastritis. The combined use of

### Table 1 Characteristics of the patients with gastric cancer in this study

| Characteristics | All patients | A | B | C | D |
|-----------------|-------------|---|---|---|---|
| No. of patients | 95          | 10| 27| 54| 4 |
| Age (yr)        | Mean (range)| 67.9 ± 8.9 (38-83) | 69.2 ± 10.0 (48-79) | 65.5 ± 9.0 (43-77) | 68.4 ± 7.6 (38-83) | 70.3 ± 6.9 (63-78) |
|                 | Median      | 69 | 70.5 | 67 | 69.5 | 70 |
| Sex             | Male/female | 72/23 | 5/5 | 19/8 | 45/9 | 3/1 |
| Location        | U/M/L       | 19/42/34 | 2/6/2 | 2/14/11 | 15/22/17 | 0/0/4 |
| Macroscopic type| Elevated/flat/depressed | 51/4/40 | 5/0/5 | 12/0/15 | 31/3/20 | 3/1/0 |
| Differentiation | Well diff/poorly diff | 76/19 | 8/2 | 18/9 | 47/7 | 3/1 |

**U**: Upper thirds of the stomach; **M**: Middle; **L**: Lower; **Well diff**: Well or moderately differentiated adenocarcinoma; **Poorly diff**: Poorly differentiated adenocarcinoma or signet ring cell carcinoma.

### Table 2 Relationship between *ABC (D)* stratification and endoscopic atrophic border in patients with gastric cancers

| ABC (D) stratification | Endoscopic atrophic border |
|------------------------|-----------------------------|
|                        | Non | Closed type | Open type | Total |
| A: *H. pylori* (+) PG (-) | 1   | 3           | 6         | 10    |
| B: *H. pylori* (+) PG (+) | 1   | 7           | 19        | 27    |
| C: *H. pylori* (+) PG (+) | 0   | 10          | 44        | 54    |
| D: *H. pylori* (+) PG (+) | 0   | 1           | 3         | 4     |
| Total                  | 2   | 21          | 72        | 95    |

*H. pylori*: *Helicobacter pylori*; PG: Pepsinogen; Non: No atrophic change.
with confirmed gastric cancers.

Rapid progress has been made in the studies on stomach carcinogenesis since the discovery of \textit{H. pylori}. The relationship between atrophic gastritis and gastric cancer has been confirmed epidemiologically. Uemura \textit{et al.}\cite{14} reported that only \textit{H. pylori}-infected subjects developed gastric cancer among a group of patients with organic or functional gastroduodenal disorders. Fukase \textit{et al.}\cite{13} reported a randomized controlled trial in which \textit{H. pylori} eradication contributed to the reduction of metachronous gastric cancer after endoscopic resection of early gastric cancer. Not surprisingly, the combination of \textit{H. pylori} infection determined by serum anti-\textit{H. pylori} antibodies and atrophic gastritis determined by serum PG levels is promising for diagnosing gastric cancer\cite{14,15}.

Mizuno \textit{et al.}\cite{16} reported that the atrophy-positive \textit{H. pylori}-positive group (group C in ABC (D) stratification system) had a moderately high hazard ratio of 11.23, while the atrophy-positive \textit{H. pylori}-negative group (group D) had a markedly higher hazard ratio of 14.81. These two groups are therefore considered the most appropriate candidates for gastric cancer screening. It is well known that anti-\textit{H. pylori} antibody production may be reduced when atrophy progresses because \textit{H. pylori} does not survive very well in the intestinal metaplasia mucosa\cite{16}. As group D represents the status of severe atrophic gastritis with marked intestinal metaplasia, it is the highest-risk group for developing gastric cancer. In addition, the atrophy-negative \textit{H. pylori}-positive group (group B) had a relatively high hazard ratio of 4.20\cite{16}. This group represents the status of \textit{H. pylori}-induced active gastritis without extensive atrophy, which is thought to be one of the factors that contribute to the diffuse-type gastric cancer. As diffuse-type gastric cancer grows and invades faster than the intestinal type, this group is considered to be a candidate for a gastric cancer screening program. In this study, there were only 3 cases in group A when group \(A'\) patients were excluded. Seven patients in group \(A'\) were receiving proton pump inhibitor therapy or had previously been treated for eradicating \textit{H. pylori} infection. As a result, precise medical interviews, such as prescription of proton pump inhibitors and a past history of \textit{H. pylori} eradication are needed. Three group A cases had mucosal atrophy upon endoscopic examination. Based on this mucosal atrophy, these cases should be classified into group D. The pepsinogen levels of these patients are shown in Table 3. In this study, the serum PG status was defined as atrophic when the criteria of both serum PG I level \(\leq 70\ \text{ng/mL}\) and a PG I / PG II ratio \(\leq 3.0\) were simultaneously fulfilled. These criteria have a sensitivity of 70.5\% and a specificity of 97\%\cite{16}. The serum PG I levels of the 3 group A cases were all \(\leq 70\ \text{ng/mL}\). They were classified into normal PG because they had a PG I / PG II ratio > 3.0. This indicates that special attention should be paid to avoiding false negative cases of atrophic gastritis. None of the gastric cancer patients in our study were both \textit{H. pylori} (-) and without atrophic gastritis. Ohata \textit{et al.}\cite{18} reported a study with a cohort of 4655 healthy asymptomatic subjects (average age,
Table 3  Summary of 10 patients with gastric cancer in group A and group A’

| Case | Stratification | Age (yr) | Sex | Location | Macroscopic type | Differentiation | PG 1/PG II levels (ng/mL) | PG I/PG II ratio | Endoscopic findings | PPI prescription | H. pylori eradication therapy |
|------|----------------|---------|-----|----------|-----------------|----------------|--------------------------|-----------------|---------------------|----------------|-----------------------------|
| 1    | A              | 70      | M   | U        | Borrmann  II     | Poor           | 28.5/7.3                 | 3.9             | Open type          | No             | No                          |
| 2    | A’             | 48      | F   | M        | II a + II c     | Well           | 55.9/8.2                 | 6.8             | Closed type        | Yes            | Yes                         |
| 3    | A              | 68      | M   | M        | II a + II c     | Well           | 64.1/11.8                | 5.4             | Open type          | No             | No                          |
| 4    | A              | 78      | F   | L        | II c            | Well           | 13.6/4.2                 | 3.2             | Closed type        | No             | No                          |
| 5    | A’             | 77      | F   | L        | II c            | Well           | 46.4/10.8                | 4.3             | Closed type        | Yes            | No                          |
| 6    | A’             | 79      | F   | M        | II a + II c     | Well           | 86.2/10.9                | 7.9             | Closed type        | Yes            | No                          |
| 7    | A              | 77      | M   | M        | LST-G           | Well           | 384.9/54.3               | 7.1             | Non                | Yes            | No                          |
| 8    | A              | 77      | F   | U        | II c            | Well           | 17.3/5.2                 | 3.3             | Open type          | No             | No                          |
| 9    | A              | 57      | M   | M        | II c            | Well           | 36.9/6.8                 | 5.4             | Open type          | No             | Yes                         |
| 10   | A’             | 71      | M   | M        | II a + II c     | Well           | 38.6/7.9                 | 4.9             | Open type          | No             | Yes                         |

H. pylori: Helicobacter pylori; PG: Pepsinogen; U: Upper thirds of the stomach; M: Middle; L: Lower; PPI: Proton pump inhibitor; Non: No atrophic change.

Table 4  Histological analysis and ABC (D) stratification based on the status of endoscopic atrophic border

| No. of patients | All patients | Male | Female | P value |
|-----------------|--------------|------|--------|---------|
| 95              | 76           | 19   | NS     |
| 95              | 76           | 19   | NS     |
| 72.23           | 58.18        | 14.5 | NS     |
| 67.9 ± 8.9      | 70.2 ± 5.8   | 61.4 ± 12.9 | < 0.05 |
| ABC (D) stratification |          |      |        |         |
| A: H. pylori (-) PG (-) | 10 (10.6%) | 8 (10.5%) | 2 (10.6%) | NS     |
| B: H. pylori (+) PG (-) | 27 (28.4%) | 19 (23.7%) | 9 (47.3%) | NS     |
| C: H. pylori (+) PG (+) | 54 (56.8%) | 47 (61.8%) | 7 (36.8%) | NS     |
| D: H. pylori (-) PG (+) | 4 (4.2%)   | 3 (3.9%)   | 1 (5.3%)   | NS     |
| Endoscopic atrophic border |          |        |        |         |
| Non             | 2 (2.1%)    | 2 (2.6%)    | 0 (0%)    | NS     |
| Closed type     | 21 (22.1%)  | 15 (19.7%)  | 6 (31.6%)  | NS     |
| Open type       | 72 (75.8%)  | 59 (77.6%)  | 13 (68.4%) | NS     |

H. pylori: Helicobacter pylori; PG: Pepsinogen; U: Upper thirds of the stomach; M: Middle; L: Lower; PPI: Proton pump inhibitor; Non: No atrophic change; Well diff: Well or moderately differentiated adenocarcinoma; Poorly diff: Poorly differentiated adenocarcinoma or signet ring cell carcinoma; NS: Not significant.

Table 5  Relationship between ABC (D) stratification and endoscopic atrophic border in histological differentiation, well differentiated adenocarcinoma

| ABC (D) stratification | Endoscopic atrophic border |
|------------------------|-----------------------------|
| Non                    | Closed type     | Open type   |
| A: H. pylori (-) PG (-) | 1          | 2           | 5           | 8 (10.5%) |
| B: H. pylori (+) PG (-) | 1          | 5           | 12          | 18 (23.7%) |
| C: H. pylori (+) PG (+) | 0          | 7           | 40          | 47 (61.8%) |
| D: H. pylori (-) PG (+) | 0          | 1           | 2           | 3 (5.3%)  |
| Total                  | 2 (2.6%)      | 15 (19.7%)  | 59 (77.6%)  | 76 (100%) |

H. pylori: Helicobacter pylori; PG: Pepsinogen; U: Upper thirds of the stomach; M: Middle; L: Lower; PPI: Proton pump inhibitor; Non: No atrophic change.

Table 6  Relationship between ABC (D) stratification and endoscopic atrophic border in histological differentiation, poorly differentiated adenocarcinoma

| ABC (D) stratification | Endoscopic atrophic border |
|------------------------|-----------------------------|
| Non                    | Closed type | Open type |
| A: H. pylori (-) PG (-) | 0          | 1         | 1       | 2 (10.6%) |
| B: H. pylori (+) PG (-) | 0          | 2         | 7       | 9 (47.4%) |
| C: H. pylori (+) PG (+) | 0          | 3         | 4       | 7 (36.8%) |
| D: H. pylori (-) PG (+) | 0          | 0         | 1       | 1 (5.3%)  |
| Total                  | 0 (0%)      | 6 (31.6%) | 13 (68.4%) | 19 (100%) |

H. pylori: Helicobacter pylori; PG: Pepsinogen; U: Upper thirds of the stomach; M: Middle; L: Lower; PPI: Proton pump inhibitor; Non: No atrophic change.

49 years) who were followed up for a mean period of 7.7 years. No cancer developed in the H. pylori (-)/normal PG group during their study period[4].

Graham and Asaka[5] proposed an eradication program for gastric cancer. Under their proposal, all adults would receive non-invasive testing for H. pylori infection and atrophic gastritis. All H. pylori infected patients would have confirmed H. pylori eradication[6]. Those with atrophic gastritis would be considered for further evaluation and possible surveillance[7]. The cases that were H. pylori (-) and had no atrophy would be excluded from the follow-up program. However, additional attention should be paid to mucosal atrophy, because the sensitivity of PG only 70.5%. Since the ultrathin transnasal endoscopy can be used for health check-ups, gastric cancer screening with ABC (D) stratification in combination with endoscopy may represent a useful screening system. In conclusion, our findings suggest that a combination screening for the H. pylori antibody titer and serum PG status may therefore be useful for predicting the development of gastric cancer. However, additional attention should be paid to avoiding false negatives for the patients who are taking acid proton pump inhibitors and those who have received prior eradication therapy for H. pylori. Endoscopy is needed for grey zone cases to accurately determine the mucosal atrophy status.

COMMENTS

Background

Gastric cancer remains the second leading cause of cancer death in Japan, although its mortality has continued to decrease for decades. Screening systems or methods to detect early gastric cancers have contributed to the decrease in gastric cancer deaths. The combination of serum pepsinogen (PG) and Helicobacter pylori (H. pylori) antibody [ABC (D) stratification] can serve as a useful predictive marker for diagnosing patients with gastric cancers.

Research frontiers

Recent studies concerning the use of ABC (D) stratification have focused on pa-
tients with either no disease or an unknown disease. There have so far been few analyses of ABC (D) stratification of patients confirmed to have gastric cancer.

**Innovations and breakthroughs**

ABC (D) stratification may be useful for predicting the development of gastric cancer. However, additional attention should be paid to avoiding false negatives for patients who are taking acid proton pump inhibitors and those who have received prior eradication therapy for H. pylori. Endoscopy is needed to evaluate grey zone cases to accurately determine the mucosal atrophy status.

**Applications**

Combination screening for the H. pylori antibody titer and serum PG status [ABC (D) stratification] is a good method for screening patients with gastric cancers.

**Terminology**

ABC (D) stratification is a screening method for patients with gastric cancer using a combination of the H. pylori antibody titer and serum PG status.

**Peer review**

This manuscript describes the evaluation of ABC (D) stratification in a group of patients confirmed to have gastric cancer. The authors found that ABC (D) stratification correlated closely with the disease status, but noted possible false negatives due to the fact that some patients have previously received treatments aimed at eradicating H. pylori. Overall, the study is well designed and the analysis approach is sound. Although the findings were somewhat expected based on previous studies, the study does provide further support for the use of the ABC (D) stratification system. The findings of this study would therefore be of interest to other researchers in this field if published.

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