

Retrospective Study

Kyoto classification in patients who developed multiple gastric carcinomas after *Helicobacter pylori* eradication

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Informed consent statement:

Patients were not required to give informed consent the study because the analysis used

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Abstract**BACKGROUND**

Endoscopic Kyoto classification predicts gastric cancer risk; however, the score in the patients with primary gastric cancer after *Helicobacter pylori* (*H. pylori*) eradication therapy is unknown.

AIM

To elucidate the Kyoto classification score in patients with both single gastric cancer and multiple gastric cancers developed after *H. pylori* eradication.

METHODS

The endoscopist recorded the Kyoto classification at the endoscope and the Kyoto classification score at the time of the first diagnosis of gastric cancer after *H. pylori* eradication. The score was compared between single gastric cancer group and multiple gastric cancers group.

anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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RESULTS

The Kyoto score at the time of diagnosis of 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the single gastric cancer group, and 5.1 points in the multiple gastric cancers group. The multiple group had a significantly higher score than the single group ($P = 0.016$). In the multiple gastric cancers group, all the patients (7/7) had 5 or higher Kyoto score, while in single gastric cancer group, the proportion of patients with a score of 5 or higher was less than half, or 44.7% (17/38).

CONCLUSION

Patients diagnosed with gastric cancer after *H. pylori* eradication tended to have advanced gastritis. In particular, in cases of multiple gastric cancers developed after *H. pylori* eradication, the endoscopic Kyoto classification score tended to be 5 or higher in patients with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

Key Words: Kyoto classification; Gastric cancer; *Helicobacter pylori*; Eradication therapy; Metachronous; Intestinal metaplasia

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Core Tip: This is a retrospective study to elucidate the endoscopic Kyoto classification score in patients with both single gastric cancer and multiple gastric cancers developed after *Helicobacter pylori* (*H. pylori*) eradication. The Kyoto score of 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the single gastric cancer group, and 5.1 points in the multiple gastric cancers group. In cases of multiple gastric cancers, the Kyoto classification score tended to be 5 or higher with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

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INTRODUCTION

Eradication therapy for *Helicobacter pylori* (*H. pylori*), which is the most important risk factor for gastric cancer, is widely conducted^[1-8]. Especially in Japan, *H. pylori* eradication therapy was approved by the national health insurance and the number of patients who received this therapy is rapidly increasing^[9]. Gastric cancer may be found even after the eradication treatment, and risk factors for gastric cancer after eradication have been vigorously examined^[6,10]. In particular, many researchers have focused on the relationship between endoscopic findings of the stomach and gastric cancer after eradication.

Recently, Kyoto classification has been devised as a method for evaluation of endoscopic findings of the stomach, and its validity is being studied^[11-14]. The Kyoto classification score is the sum of scores for five endoscopic findings (atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness) and ranges from 0 to 8. Atrophy, intestinal metaplasia, enlarged folds, and nodularity contribute to gastric cancer risk. Diffuse redness and regular arrangement of collecting venules (RACs) are related to *H. pylori* infection status^[13,15]. Toyoshima *et al*^[13] described that a Kyoto classification score ≥ 2 indicates *H. pylori* infection, and a Kyoto classification score ≥ 4 might indicate gastric cancer risk.

On the other hand, gastric cancer treatment is becoming less invasive, and the rate of treatment by local excision has increased^[16-19]. With local treatment of the stomach, recurrence of gastric cancer can occur^[20,21]. Although there is a relatively large number of reports on metachronous gastric cancer occurrence after *H. pylori* eradication therapy following endoscopic treatment for gastric cancer (gastric cancer diagnosis,

endoscopic treatment, *H. pylori* eradication, metachronous gastric cancer), there are few reports of multiple primary gastric cancers found after *H. pylori* eradication therapy (*H. pylori* eradication, multiple primary gastric cancer). As described above, with the spread of eradication therapy for *H. pylori*, the number of patients with gastric cancer diagnosed for the first time after eradication therapy is on the rise; therefore, the analysis of these cases would become more important. If gastric cancers are discovered during follow-up after the detection of primary stomach cancers, it is essentially difficult to distinguish whether those cancers occurred simultaneously or appeared at different time points since the growth speed of each gastric cancer would be different^[22]. In the present study, synchronous gastric cancers and metachronous gastric cancers were collectively treated as multiple gastric cancers. As far as we know, few data exist on the association between Kyoto classification and primary gastric cancer occurrence post *H. pylori* eradication therapy. The purpose of this study was to develop Kyoto classification for differentiating between single and multiple gastric cancers in patients diagnosed with gastric cancer after *H. pylori* eradication.

MATERIALS AND METHODS

Study outline and patients

This retrospective study included 67 patients who were diagnosed with primary gastric cancer at least six months after the successful *H. pylori* eradication therapy between February 2010 to February 2019 in Toyoshima Endoscopy Clinic. We used data available from clinical charts and endoscopic database. We defined primary gastric cancer as pathologically diagnosed gastric cancer without past gastric neoplasm history. We divided these 67 gastric cancer patients into single gastric cancer patients and multiple gastric cancer patients. We defined multiple gastric cancer patients as those who had synchronous and/or metachronous gastric cancer. Patients without one or more follow-up endoscopy at our institution after primary gastric cancer diagnosis were excluded from the single gastric cancer patient group. This retrospective study was approved by the Ethical Review Committee of Hattori Clinic on September 6, 2019 (approval No. S1909-U06). Written informed consent was obtained from all patients. All clinical investigations were conducted according to the ethical guidelines of the Declaration of Helsinki.

***H. pylori* eradication therapy**

Patients in whom *H. pylori* infection was confirmed underwent eradication therapy as described in our previous reports^[5,23]. Patients who failed eradication therapy, received an additional treatment: First-line therapy included proton pump inhibitor (PPI), amoxicillin, and clarithromycin. Second-line therapy consisted of PPI, amoxicillin, and metronidazole. At least four weeks after the eradication therapy was completed, cure status was confirmed by ¹³C urea breath test.

Endoscopic procedure and Kyoto classification

Esophagogastroduodenoscopy was performed by certificated endoscopists. The patients underwent esophagogastroduodenoscopy either for screening, for a previous history of esophagogastroduodenal disease, present symptoms or abnormal findings on barium meal examination. Biopsy specimens were taken from lesions suspected to be gastric cancer, and the final diagnosis of gastric cancer was based on pathology results^[3]. The endoscopists who performed each endoscopic procedure recorded the Kyoto classification of the endoscopic findings and the Kyoto classification score at the time of the first diagnosis of gastric cancer after *H. pylori* eradication was used for the analysis. A board certificated endoscopist reviewed each item of the Kyoto classification score. If there was a discrepancy in opinion, the final score was decided by joint discussion. The Kyoto classification of gastritis was based on the sum of the following five endoscopic scores using the range from 0 to 8. Gastric atrophy was classified according to the degree of mucosal atrophy as described by Kimura and Takemoto^[20] with the Kimura-Takemoto classification of C-II and C-III scored as 1 while that of O-I to O-III scored as 2. Intestinal metaplasia was observed as grayish-whitish and slightly opalescent patches; intestinal metaplasia in the antrum was scored as 1 and intestinal metaplasia that was spread to the corpus was scored as 2. The presence of a fold that expanded to more than 5 mm was scored as 1. Nodularity was characterized by the appearance of multiple white raised lesions in the pyloric gland mucosa, and the presence of nodularity was scored as 1^[24,25]. Diffuse redness referred to uniform redness involving the entire fundic gland mucosa, and the presence of diffuse

redness with RACs was rated as 1 and without RACs as 2^[10,15]. After the diagnosis of gastric cancer, the tumor size, histological type, the Union for International Cancer Control cancer stage, and treatment modality were recorded in clinical chart and database.

Statistical analyses

All statistical analyses were performed using JMP10 software (SAS Institute, Cary, NC, USA). Welch's *t* test was used to compare the means of continuous variables. Comparisons of nominal variables were performed using the χ^2 test or Fisher's exact test, as appropriate. A two-sided *P* value of < 0.05 was considered to indicate statistical significance.

RESULTS

Of those diagnosed with gastric cancers at the Toyoshima Endoscope Clinic, 67 patients underwent eradication of *H. pylori* at least six months before the diagnosis, had no history of gastric cancer before eradication, and had no history of gastrectomy (the average observation period after eradication was 2.4 years). Seven cases of multiple gastric cancer were found (Table 1). In the multiple gastric cancers group, almost all the patients (6/7) had 5 points Kyoto score and one patient had 6 points Kyoto score. Three of these were metachronous gastric carcinomas and all of these patients had synchronous gastric carcinomas. In the three metachronous cases, the observation period from the primary gastric cancer diagnosis after *H. pylori* eradication therapy to the discovery of metachronous gastric cancer averaged 3.7 years.

We diagnosed 60 patients with primary gastric cancer after *H. pylori* eradication therapy. Of these, 22 patients without multiple gastric carcinomas (with the primary gastric cancer detected on average at 2.7 years after eradication) did not undergo follow-up endoscopy in the Toyoshima Endoscopy Clinic and were excluded. The remaining 38 patients received at least one follow-up endoscopy after the primary gastric cancer diagnosis so as to confirm the lack of multiple gastric cancer occurrence (mean observation period between primary gastric cancer diagnosis and the last follow-up endoscopy was 4.3 years); these were defined as single gastric cancer patients. Thus, patients with gastric cancer after *H. pylori* eradication were divided into single gastric cancer patients group (Single, 38 patients) and multiple gastric cancer patients group (Multiple, 7 patients) in the final analysis.

The baseline characteristics of the 45 gastric cancer patients that included 17 males and 28 females, with mean age of 67.0 years (range 43-86) are provided in Table 2. For these 45 cases, it took an average of 5.0 years from *H. pylori* eradication to the discovery of cancer. There was no difference in male to female ratio between single and Multiple groups, with the average age being higher in the Multiple group (65.6 years and 74.7 years, respectively, *P* = 0.039). The Kyoto score at the time of detection in 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the Single group, and 5.1 points in the Multiple group. The Multiple group had a higher score with a statistically significant difference (*P* = 0.016). In the Multiple gastric cancer group, all of the patients had 5 or higher Kyoto score, while in a Single gastric cancer group, the proportion of patients with a score of 5 or higher was less than half, or 44.7% (17/38). Enlarged folds, nodularity, and diffuse redness without RACs, the findings to suggest active *H. pylori* infection, were rarely observed [6.66% (3/45), 0, and 2.22% (1/45), respectively] in the background gastric mucosa in the 45 patients diagnosed with gastric cancer after successful *H. pylori* eradication therapy. All of the patients in multiple gastric cancer group had an open type atrophy and intestinal metaplasia of the corpus as background gastric mucosa. In the Single gastric cancer group, 68.2% (26/38) of the patients had an open type atrophy. Regarding intestinal metaplasia in the Single gastric cancer group, 31.5% (12/38) of the patients had no intestinal metaplasia, 21.0% (8/38) had intestinal metaplasia within antrum, and 47.3% (18/38) had corpus intestinal metaplasia. Map like redness was observed in 56.4% (22/38) and 71.4% (5/7) of the patients in Single and Multiple gastric cancer groups, respectively. Of the 45 cases of gastric cancer diagnosis after the eradication, most were graded as stage I (95.5% excluding 2 cases), pathologically grouped as intestinal type gastric cancer (93.3% excluding 3 diffuse type gastric cancer), and underwent curative endoscopic treatment (95.5% excluding 2 surgical cases). There was no difference in cancer size, stage, pathology, and treatment modality between the Single and Multiple groups.

Table 1 Characteristics of 7 cases of multiple gastric cancers after *Helicobacter pylori* eradication

Case	Sex	Age (yr), number of diagnosed lesions	Age (yr), number of diagnosed lesions
1	Female	79, 2	84, 1
2	Male	84, 2	87, 1
3	Female	71, 2	
4	Male	74, 1	77, 2
5	Male	71, 2	
6	Male	81, 3	
7	Male	63, 2	

DISCUSSION

In this examination, we aimed to elucidate the endoscopic Kyoto score in patients with single and multiple gastric cancer after *H. pylori* eradication. We showed that patients who were diagnosed with gastric cancer after *H. pylori* eradication, had high Kyoto classification score of 4.0 on average, and in particular, multiple gastric cancer patients had an even higher score of 5.1. This result is in line with those shown in previous papers that argued about the importance of endoscopic follow-up even after the eradication of *H. pylori*, especially in advanced cases of gastritis^[5,26,27].

In our analysis, most of the post *H. pylori* eradication gastric cancers were the intestinal type, was consistent with the findings in past reports^[3,28,29]. Intestinal type gastric cancers are often surrounded by intestinal metaplasia as background gastric mucosa^[30], and intestinal metaplasia is reportedly well known risk factor for metachronous gastric cancer^[6,10,31]. Endoscopic gastritis grading, Kimura-Takemoto classification is also a very well-established classification that well describes the risk of gastric cancer, including gastric cancer after eradication^[27,32,33]. In the Kyoto classification, positive findings on the items such as enlarged folds, nodularity, and diffuse redness are tended to disappear *via H. pylori* eradication therapy. On the other hand, both advanced intestinal metaplasia and atrophic gastritis, which have been established as risk factors for gastric cancer, did not improve in a short period of time^[34]. We believe that multiple gastric carcinomas could occur in the situation of so called "point of no return", in which gastric carcinogenesis cascade had progressed to the advanced stage due to the *H. pylori* infection; therefore, even the eradication therapy could not repair the molecularly irreversible gastric mucosal changes^[35,36].

This study has limitations. First, the study was conducted at a single institute and included a small number of patients. Future large scale and matched study is needed. Second, future longer observation could make some single gastric cancer cases into multiple cancer cases. Third, though we used Kyoto score at the time of primary cancer diagnosis, the score could change in the time course after the *H. pylori* eradication. Fourth, several possible confounding factors including dietary habits, family genetic history, and *H. pylori* virulent factors are not included in this examination.

In conclusion, patients diagnosed with gastric cancer after *H. pylori* eradication tended to have advanced gastritis. In particular, in cases of multiple gastric cancers after eradication, the endoscopic Kyoto classification score tended to be at least 5 or higher with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

Table 2 Characteristics of the 45 gastric cancer after *Helicobacter pylori* eradication

Characteristics	Total (n = 45)	Single (n = 38)	Multiple (n = 7)	P value
Mean age (range), yr	67.0 (43-86)	65.6 (43-86)	74.7 (63-84)	0.039 ^a
Sex, n (%)				0.61
Female	17 (37.7)	15 (39.4)	2 (28.5)	
Male	28 (62.2)	23 (60.5)	5 (71.4)	
Kyoto score, average	4.02	3.81	5.14	0.016 ^a
Atrophic gastritis, score, n (%)	1.71	1.65	2.00	0.77
None, 0	1 (2.22)	1 (2.63)	0	
C-1, 0	0	0	0	
C-2, 1	7 (15.5)	7 (18.4)	0	
C-3, 1	4 (8.88)	4 (10.5)	0	
O-1, 2	7 (15.5)	6 (15.7)	1 (14.2)	
O-2, 2	7 (15.5)	6 (15.7)	1 (14.)	
O-3, 2	19 (42.2)	14 (36.8)	5 (71.4)	
Intestinal metaplasia, score, n (%)	1.28	1.15	2.00	0.048 ^a
None, 0	12 (26.6)	12 (31.5)	0	
Antrum, 1	8 (17.7)	8 (21.0)	0	
Corpus, 2	25 (55.5)	18 (47.3)	7 (100)	
Enlarged folds, score, n (%)	0.06	0.07	0	0.44
None, 0	42 (93.3)	35 (92.1)	7 (100)	
Present, 1	3 (6.66)	3 (7.89)	0	
Nodularity, score, n (%)	0	0	0	1.00
None, 0	45 (100)	38 (100)	7 (100)	
Present, 1	0	0	0	
Diffuse redness, score, n (%)	0.95	0.92	1.14	0.65
None, 0	3 (6.66)	3 (7.89)	0	
With RAC, 1	41 (91.1)	35 (92.1)	6 (85.7)	
Without RAC, 2	1 (2.22)	0	1 (14.2)	
Map like redness, yes	27 (58.6)	22 (56.4)	5 (71.4)	0.68
Mean size (range), mm	14.8 (1.0-120)	15.5 (1-120)	11.1 (1.0-35)	0.46
Pathology, n (%)				
Intestinal type	42 (93.3)	35 (92.1)	7 (100)	0.44
Diffuse type	3 (6.66)	3 (7.89)	0	
Stage, n (%)				0.98
I	43 (95.5)	36 (94.7)	7 (100)	
II	1 (2.22)	1 (2.63)	0	
III	1 (2.22)	1 (2.63)	0	
IV	0	0	0	
Treatment for gastric cancer, n (%)				
Endoscopy	43 (95.5)	36 (94.7)	7 (100)	0.54
Surgery	2 (4.44)	2 (5.26)	0	
Chemotherapy	0	0	0	

Best supportive care

0

0

0

^aStatistically significant. RAC: Regular arrangement of collecting venule.

ARTICLE HIGHLIGHTS

Research background

With the spread of eradication therapy for *Helicobacter pylori* (*H. pylori*), the number of patients with gastric cancer diagnosed for the first time after eradication therapy is on the rise; therefore, the analysis of these cases would become more important. Recently, Kyoto classification has been devised as a method for evaluation of endoscopic findings of the stomach, and its validity is being studied.

Research motivation

As far as we know, few data exist on the association between Kyoto classification and primary gastric cancer occurrence post *H. pylori* eradication therapy.

Research objectives

The purpose of this study was to develop Kyoto classification for differentiating between single and multiple gastric cancers in patients diagnosed with gastric cancer after *H. pylori* eradication.

Research methods

This retrospective study included 67 patients who were diagnosed with primary gastric cancer at least six months after the successful *H. pylori* eradication therapy between February 2010 to February 2019 in Toyoshima Endoscopy Clinic. We used data available from clinical charts and endoscopic database. We defined primary gastric cancer as pathologically diagnosed gastric cancer without past gastric neoplasm history. We divided these 67 gastric cancer patients into single gastric cancer patients and multiple gastric cancer patients. We defined multiple gastric cancer patients as those who had synchronous and/or metachronous gastric cancer. Patients without one or more follow-up endoscopy at our institution after primary gastric cancer diagnosis were excluded from the single gastric cancer patient group.

Research results

The Kyoto score at the time of diagnosis of 45 cases of gastric cancer after *H. pylori* eradication was 4.0 points in average. The score was 3.8 points in the single gastric cancer group, and 5.1 points in the multiple gastric cancers group. The multiple group had a significantly higher score than the single group ($P = 0.016$). In the multiple gastric cancers group, all the patients (7/7) had 5 or higher Kyoto score, while in single gastric cancer group, the proportion of patients with a score of 5 or higher was less than half, or 44.7% (17/38).

Research conclusions

Patients diagnosed with gastric cancer after *H. pylori* eradication tended to have advanced gastritis. In particular, in cases of multiple gastric cancers developed after *H. pylori* eradication, the endoscopic Kyoto classification score tended to be 5 or higher in patients with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.

Research perspectives

We believe that multiple gastric carcinomas could occur in the situation of so called "point of no return", in which gastric carcinogenesis cascade had progressed to the advanced stage due to the *H. pylori* infection; therefore, even the eradication therapy could not repair the molecularly irreversible gastric mucosal changes.

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