ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2020 September 16; 12(9): 256-322

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 12 Number 9 September 16, 2020

EXPERT RECOMMENDATIONS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

CASE REPORT

LETTER TO THE EDITOR

World Journal of Gastrointestinal Endoscopy

Monthly Volume 12 Number 9 September 16, 2020

Contents

ABOUT COVER

Editor-in-Chief of *World Journal of Gastrointestinal Endoscopy*, Dr. Sang Chul Lee is a Professor in the Department of General Surgery of the College of Medicine, Catholic University of Korea and a Colorectal Surgeon at Daejeon St. Mary's Hospital, which is famous for minimally invasive surgery in Korea. His clinical practice specialization in laparoscopic surgery involves a focus in the field of single-port laparoscopic techniques. His standard and routine operation modality is single-port laparoscopic SOLO surgery, with application in a vast spectrum of disease entities and conducted by use of a camera-holder instead of a human assistant. His ongoing research interests are minimally invasive surgery and endoscopic procedures, and for the last several years, he has been performing completely scar-less surgeries. He serves as editorial board member and reviewer for several scientific journals and has published more than 120 peer-reviewed articles. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE
September 16, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2020 September 16; 12(9): 276-284

DOI: 10.4253/wjge.v12.i9.276

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

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

Kosuke Sakitani, Toshihiro Nishizawa, Akira Toyoshima, Shuntaro Yoshida, Tatsuya Matsuno, Tomoharu Yamada, Masatoshi Irokawa, Yoshiyuki Takahashi, Yousuke Nakai, Osamu Toyoshima, Kazuhiko Koike

ORCID number: Kosuke Sakitani 0000-0002-4537-6023; Toshihiro Nishizawa 0000-0003-4876-3384; Akira Toyoshima 0000-0002-5697-6251; Shuntaro Yoshida 0000-0002-9437-9132; Tatsuya Matsuno 0000-0002-1935-3506; Tomoharu Yamada 0000-0001-6312-5706; Masatoshi Irokawa 0000-0002-5089-8619; Yoshiyuki Takahashi 0000-0002-6724-8057; Yousuke Nakai 0000-0001-7411-1385; Osamu Toyoshima 0000-0002-6953-6079; Kazuhiko Koike 0000-0002-9739-9243.

Author contributions: Sakitani K wrote the manuscript; Sakitani K, Nishizawa T, Toyoshima A, Yoshida S, Matsuno T, Yamada T, Irokawa M, Takahashi Y, Toyoshima O collected and analyzed the data and revised the manuscript; Nakai Y, Koike K and Toyoshima O supervised the study; Toyoshima O conceived and designed the study.

Institutional review board statement: This retrospective study was approved by the Ethical Review Committee of Hattori Clinic on September 6, 2019 (approval no. S1909-U06).

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

Kosuke Sakitani, Toshihiro Nishizawa, Shuntaro Yoshida, Tatsuya Matsuno, Tomoharu Yamada, Masatoshi Irokawa, Yoshiyuki Takahashi, Osamu Toyoshima, Department of Gastroenterology, Toyoshima Endoscopy Clinic, Tokyo 157-0066, Japan

Kosuke Sakitani, Department of Gastroenterology, Sakitani Endoscopy Clinic, Chiba 275-0026, Japan

Toshihiro Nishizawa, Department of Gastroenterology, International University of Health and Welfare, Narita Hospital, Chiba, 286-8520, Japan

Akira Toyoshima, Department of Colorectal Surgery, Japanese Red Cross Medical Center, Tokyo 150-8935, Japan

Tatsuya Matsuno, Tomoharu Yamada, Yousuke Nakai, Osamu Toyoshima, Kazuhiko Koike, Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, Tokyo 113-8655, Japan

Corresponding author: Osamu Toyoshima, MD, Doctor, Department of Gastroenterology, Toyoshima Endoscopy Clinic, 6-17-5 Seijo, Setagaya-ku, Tokyo 157-0066, Japan. t@ichou.com

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.

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

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.

Citation: Sakitani K, Nishizawa T, Toyoshima A, Yoshida S, Matsuno T, Yamada T, Irokawa M, Takahashi Y, Nakai Y, Toyoshima O, Koike K. Kyoto classification in patients who developed multiple gastric carcinomas after *Helicobacter pylori* eradication. *World J Gastrointest Endosc* 2020; 12(9): 276-284
URL: https://www.wjgnet.com/1948-5190/full/v12/i9/276.htm
DOI: https://dx.doi.org/10.4253/wjge.v12.i9.276

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 indicates 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,

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

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Received: June 10, 2020
Peer-review started: June 10, 2020
First decision: July 21, 2020
Revised: July 29, 2020
Accepted: August 15, 2020
Article in press: August 15, 2020
Published online: September 16, 2020

P-Reviewer: Emara M, Gao F
S-Editor: Yan JP
L-Editor: A
P-Editor: Li JH

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 ^{13}C 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

[a]Statistically 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.

ACKNOWLEDGEMENTS

The authors thank the gastroenterologists who performed the endoscopic procedures at the Toyoshima Endoscopy Clinic (Tokyo, Japan).

REFERENCES

1 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]

2 **Fukase K**, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M; Japan Gast Study Group. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372**: 392-397 [PMID: 18675689 DOI: 10.1016/S0140-6736(08)61159-9]

3 **Sakitani K**, Hirata Y, Suzuki N, Shichijo S, Yanai A, Serizawa T, Sakamoto K, Akanuma M, Maeda S, Yamaji Y, Iwamoto Y, Kawazu S, Koike K. Gastric cancer diagnosed after Helicobacter pylori eradication in diabetes mellitus patients. *BMC Gastroenterol* 2015; **15**: 143 [PMID: 26486595 DOI: 10.1186/s12876-015-0377-0]

4 **Nishizawa T**, Suzuki H, Arano T, Yoshida S, Yamashita H, Hata K, Kanai T, Yahagi N, Toyoshima O. Characteristics of gastric cancer detected within 1 year after successful eradication of *Helicobacter pylori*. *J Clin Biochem Nutr* 2016; **59**: 226-230 [PMID: 27895391 DOI: 10.3164/jcbn.16-43]

5 **Sakitani K**, Nishizawa T, Arita M, Yoshida S, Kataoka Y, Ohki D, Yamashita H, Isomura Y, Toyoshima A, Watanabe H, Iizuka T, Saito Y, Fujisaki J, Yahagi N, Koike K, Toyoshima O. Early detection of gastric cancer after Helicobacter pylori eradication due to endoscopic surveillance. *Helicobacter* 2018; **23**: e12503 [PMID: 29924436 DOI: 10.1111/hel.12503]

6 **Choi JM**, Kim SG, Choi J, Park JY, Oh S, Yang HJ, Lim JH, Im JP, Kim JS, Jung HC. Effects of Helicobacter pylori eradication for metachronous gastric cancer prevention: a randomized controlled trial. *Gastrointest Endosc* 2018; **88**: 475-485.e2 [PMID: 29800546 DOI: 10.1016/j.gie.2018.05.009]

7 **Choi IJ**, Kim CG, Lee JY, Kim YI, Kook MC, Park B, Joo J. Family History of Gastric Cancer and *Helicobacter pylori* Treatment. *N Engl J Med* 2020; **382**: 427-436 [PMID: 31995688 DOI: 10.1056/NEJMoa1909666]

8 **Enomoto S**, Maekita T, Ohata H, Yanaoka K, Oka M, Ichinose M. Novel risk markers for gastric cancer screening: Present status and future prospects. *World J Gastrointest Endosc* 2010; **2**: 381-387 [PMID: 21191511 DOI: 10.4253/wjge.v2.i12.381]

9 **Asaka M**, Kato M, Sakamoto N. Roadmap to eliminate gastric cancer with Helicobacter pylori eradication and consecutive surveillance in Japan. *J Gastroenterol* 2014; **49**: 1-8 [PMID: 24162382 DOI: 10.1007/s00535-013-0897-8]

10 **Mori G**, Nakajima T, Asada K, Shimazu T, Yamamichi N, Maekita T, Yokoi C, Fujishiro M, Gotoda T, Ichinose M, Ushijima T, Oda I. Incidence of and risk factors for metachronous gastric cancer after endoscopic resection and successful Helicobacter pylori eradication: results of a large-scale, multicenter cohort study in Japan. *Gastric Cancer* 2016; **19**: 911-918 [PMID: 26420267 DOI: 10.1007/s10120-015-0544-6]

11 **Nishizawa T**, Sakitani K, Suzuki H, Yamakawa T, Takahashi Y, Yamamichi N, Watanabe H, Seto Y, Koike K, Toyoshima O. A combination of serum anti-*Helicobacter pylori* antibody titer and Kyoto classification score could provide a more accurate diagnosis of *H pylori*. *United European Gastroenterol J* 2019; **7**: 343-348 [PMID: 31019702 DOI: 10.1177/2050640619825947]

12 **Shichijo S**, Hirata Y, Niikura R, Hayakawa Y, Yamada A, Koike K. Association between gastric cancer and the Kyoto classification of gastritis. *J Gastroenterol Hepatol* 2017; **32**: 1581-1586 [PMID: 28217843 DOI: 10.1111/jgh.13764]

13 **Toyoshima O**, Nishizawa T, Koike K. Endoscopic Kyoto classification of *Helicobacter pylori* infection and gastric cancer risk diagnosis. *World J Gastroenterol* 2020; **26**: 466-477 [PMID: 32089624 DOI: 10.3748/wjg.v26.i5.466]

14 **Yoshii S**, Mabe K, Watano K, Ohno M, Matsumoto M, Ono S, Kudo T, Nojima M, Kato M, Sakamoto N. Validity of endoscopic features for the diagnosis of Helicobacter pylori infection status based on the Kyoto classification of gastritis. *Dig Endosc* 2020; **32**: 74-83 [PMID: 31309632 DOI: 10.1111/den.13486]

15 **Alaboudy A**, Elbahrawy A, Matsumoto S, Galal GM, Chiba T. Regular arrangement of collecting venules: Does patient age affect its accuracy? *World J Gastrointest Endosc* 2011; **3**: 118-123 [PMID: 21860679 DOI: 10.4253/wjge.v3.i6.118]

16 **Nishizawa T**, Yahagi N. Endoscopic mucosal resection and endoscopic submucosal dissection: technique and new directions. *Curr Opin Gastroenterol* 2017; **33**: 315-319 [PMID: 28704212 DOI: 10.1097/MOG.0000000000000388]

17 **Tsuji K**, Yoshida N, Nakanishi H, Takemura K, Yamada S, Doyama H. Recent traction methods for endoscopic submucosal dissection. *World J Gastroenterol* 2016; **22**: 5917-5926 [PMID: 27468186 DOI: 10.3748/wjg.v22.i26.5917]

18 **Fujishiro M**, Yoshida S, Matsuda R, Narita A, Yamashita H, Seto Y. Updated evidence on endoscopic resection of early gastric cancer from Japan. *Gastric Cancer* 2017; **20**: 39-44 [PMID: 27704225 DOI: 10.1007/s10120-016-0647-8]

19 **Akintoye E**, Obaitan I, Muthusamy A, Akanbi O, Olusunmade M, Levine D. Endoscopic submucosal dissection of gastric tumors: A systematic review and meta-analysis. *World J Gastrointest Endosc* 2016; **8**: 517-532 [PMID: 27606044 DOI: 10.4253/wjge.v8.i15.517]

20 **Nishizawa T**, Yahagi N. Long-Term Outcomes of Using Endoscopic Submucosal Dissection to Treat Early Gastric Cancer. *Gut Liver* 2018; **12**: 119-124 [PMID: 28673068 DOI: 10.5009/gnl17095]

21 **Okada K**, Suzuki S, Naito S, Yamada Y, Haruki S, Kubota M, Nakajima Y, Shimizu T, Ando K, Uchida Y, Hirasawa T, Fujisaki J, Tsuchida T. Incidence of metachronous gastric cancer in patients whose primary gastric neoplasms were discovered after Helicobacter pylori eradication. *Gastrointest Endosc* 2019; **89**: 1152-1159.e1 [PMID: 30825537 DOI: 10.1016/j.gie.2019.02.026]

22 **Choi IJ**, Kim YI, Park B. Helicobacter pylori and Prevention of Gastric Cancer. *N Engl J Med* 2018; **378**: 2244-2245 [PMID: 29874533 DOI: 10.1056/NEJMc1805129]

23 **Toyoshima O**, Yamaji Y, Yoshida S, Matsumoto S, Yamashita H, Kanazawa T, Hata K. Endoscopic gastric atrophy is strongly associated with gastric cancer development after Helicobacter pylori eradication. *Surg*

Endosc 2017; **31**: 2140-2148 [PMID: 27604367 DOI: 10.1007/s00464-016-5211-4]
24 **Albuquerque A**. Nodular lymphoid hyperplasia in the gastrointestinal tract in adult patients: A review. *World J Gastrointest Endosc* 2014; **6**: 534-540 [PMID: 25400867 DOI: 10.4253/wjge.v6.i11.534]
25 **Toyoshima O**, Nishizawa T, Sakitani K, Yamakawa T, Watanabe H, Yoshida S, Nakai Y, Hata K, Ebinuma H, Suzuki H, Koike K. Nodularity-like appearance in the cardia: novel endoscopic findings for *Helicobacter pylori* infection. *Endosc Int Open* 2020; **8**: E770-E774 [PMID: 32490162 DOI: 10.1055/a-1136-9890]
26 **Shichijo S**, Hirata Y, Sakitani K, Yamamoto S, Serizawa T, Niikura R, Watabe H, Yoshida S, Yamada A, Yamaji Y, Ushiku T, Fukayama M, Koike K. Distribution of intestinal metaplasia as a predictor of gastric cancer development. *J Gastroenterol Hepatol* 2015; **30**: 1260-1264 [PMID: 25777777 DOI: 10.1111/jgh.12946]
27 **Shichijo S**, Hirata Y, Niikura R, Hayakawa Y, Yamada A, Ushiku T, Fukayama M, Koike K. Histologic intestinal metaplasia and endoscopic atrophy are predictors of gastric cancer development after Helicobacter pylori eradication. *Gastrointest Endosc* 2016; **84**: 618-624 [PMID: 26995689 DOI: 10.1016/j.gie.2016.03.791]
28 **Kamada T**, Hata J, Sugiu K, Kusunoki H, Ito M, Tanaka S, Inoue K, Kawamura Y, Chayama K, Haruma K. Clinical features of gastric cancer discovered after successful eradication of Helicobacter pylori: results from a 9-year prospective follow-up study in Japan. *Aliment Pharmacol Ther* 2005; **21**: 1121-1126 [PMID: 15854174 DOI: 10.1111/j.1365-2036.2005.02459.x]
29 **Sakitani K**, Hirata Y, Watabe H, Yamada A, Sugimoto T, Yamaji Y, Yoshida H, Maeda S, Omata M, Koike K. Gastric cancer risk according to the distribution of intestinal metaplasia and neutrophil infiltration. *J Gastroenterol Hepatol* 2011; **26**: 1570-1575 [PMID: 21575058 DOI: 10.1111/j.1440-1746.2011.06767.x]
30 **Lauren P**. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675 DOI: 10.1111/apm.1965.64.1.31]
31 **Shiotani A**, Uedo N, Iishi H, Yoshiyuki Y, Ishii M, Manabe N, Kamada T, Kusunoki H, Hata J, Haruma K. Predictive factors for metachronous gastric cancer in high-risk patients after successful Helicobacter pylori eradication. *Digestion* 2008; **78**: 113-119 [PMID: 19023205 DOI: 10.1159/000173719]
32 **Take S**, Mizuno M, Ishiki K, Yoshida T, Ohara N, Yokota K, Oguma K, Okada H, Yamamoto K. The long-term risk of gastric cancer after the successful eradication of Helicobacter pylori. *J Gastroenterol* 2011; **46**: 318-324 [PMID: 21103997 DOI: 10.1007/s00535-010-0347-9]
33 **Masuyama H**, Yoshitake N, Sasai T, Nakamura T, Masuyama A, Zuiki T, Kurashina K, Mieda M, Sunada K, Yamamoto H, Togashi K, Terano A, Hiraishi H. Relationship between the degree of endoscopic atrophy of the gastric mucosa and carcinogenic risk. *Digestion* 2015; **91**: 30-36 [PMID: 25632914 DOI: 10.1159/000368807]
34 **Kodama M**, Okimoto T, Ogawa R, Mizukami K, Murakami K. Endoscopic atrophic classification before and after H. pylori eradication is closely associated with histological atrophy and intestinal metaplasia. *Endosc Int Open* 2015; **3**: E311-E317 [PMID: 26357676 DOI: 10.1055/s-0034-1392090]
35 **Wong BC**, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS; China Gastric Cancer Study Group. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194 [PMID: 14722144 DOI: 10.1001/jama.291.2.187]
36 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com