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Contents

Thrice Monthly Volume 12 Number 14 May 16, 2024

EDITORIAL

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

Retrospective Study

Clinical and Translational Research

CASE REPORT

LETTER TO THE EDITOR

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Contents

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ORIGINAL ARTICLE

Retrospective Study

Non-improvement of atrophic gastritis in cases of gastric cancer after successful *Helicobacter pylori* eradication therapy

Yuto Suzuki, Yasumi Katayama, Yo Fujimoto, Ikuhiro Kobori, Masaya Tamano

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) infection is closely related to the development of gastric cancer (GC). However, GC can develop even after *H. pylori* eradication. Therefore, it would be extremely useful if GC could be predicted after eradication. The Kyoto classification score for gastritis (GA) is closely related to cancer risk. However, how the score for GC changes after eradication before onset is not well understood.

AIM

To investigate the characteristics of the progression of Kyoto classification scores for GC after *H. pylori* eradication.

METHODS

Eradication of *H. pylori* was confirmed in all patients using either the urea breath test or the stool antigen test. The Kyoto classification score of GC patients was evaluated by endoscopy at the time of event onset and three years earlier. In addition, the modified atrophy score was evaluated and compared between the GC group and the control GA group.

RESULTS

In total, 30 cases of early GC and 30 cases of chronic GA were evaluated. The pathology of the cancer cases was differentiated adenocarcinoma, except for one case of undifferentiated adenocarcinoma. The total score of the Kyoto classification was significantly higher in the GC group both at the time of cancer onset and three years earlier (4.97 *vs* 3.73, $P = 0.0034$; 4.2 *vs* 3.1, $P = 0.0035$, respectively). The modified atrophy score was significantly higher in the GC group both at the

time of cancer onset and three years earlier and was significantly improved only in the GA group (5.3 *vs* 5.3, P = 0.5; 3.73 *vs* 3.1, P = 0.0475, respectively).

CONCLUSION

The course of the modified atrophy score is useful for predicting the onset of GC after eradication. Patients with severe atrophy after *H. pylori* eradication require careful monitoring.

Key Words: *Helicobacter pylori*; Kyoto classification; Gastritis; Eradication therapy; Gastric cancer

Core Tip: *Helicobacter pylori* (*H. pylori)* infection is closely related to the development of gastric cancer (GC). Therefore, *H. pylori* eradication therapy is very important. However, GC can develop even after *H. pylori* eradication. Thus, it would be very useful if the onset of GC could be predicted. The Kyoto classification of gastritis is useful for endoscopic diagnosis. In this study, we showed that a modified atrophy score may be useful for predicting GC after eradication. In cases of GC after eradication, the modified atrophy score did not decrease during endoscopic follow-up. Gastric mucosal atrophic findings should be noted during post-eradication surveillance.

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INTRODUCTION

In 1983, *Helicobacter pylori (H. pylori*) was successfully isolated and cultured, and this bacterium was found to be the cause of histological gastritis (GA)[1]. Accumulation of genetic abnormalities due to persistent inflammation leads to gastric carcinogenesis[2]. Many studies, basic, clinical, and epidemiological, have shown the relationship between *H. pylori* and gastric cancer (GC)[3-5]. Though eradication of *H. pylori* prevents GC development[6]. The incidence of GC does not completely disappear after eradication[7]. Therefore, it is very important to identify risk factors for carcinogenesis during post-eradication surveillance. The most reliable method may be to screen for genetic mutations and methylation levels in gastric mucosa[6,8]. Methylation levels of certain microRNAs after eradication are associated with an increased risk of developing metachronous GC[9]. However, this method cannot yet be easily used in general practice. Therefore, regular endoscopy after eradication is important.

The Kyoto classification of GA aims to predict the onset of GC by scoring and evaluating the mucosal condition of GA [10]. It can be easily scored using an endoscope, and there have been several reports of the usefulness of the score at the onset of GC [11]. We have also reported that scores obtained several years before the onset of GC are useful for predicting the subsequent onset of GC[12]. However, its usefulness for predicting GC after eradication is unknown. In this study, whether the time course of Kyoto classification scores for GC after eradication shows any specific characteristic was investigated.

MATERIALS AND METHODS

Patients and settings

Patients were selected from among cases who underwent endoscopic submucosal dissection (ESD) for GC after eradication at our hospital from 2015 to 2023. Patients who developed cancer more than five years after eradication and who had undergone endoscopy three years before the onset of cancer were considered (Figure 1). As controls, cases of GA diagnosed by upper gastrointestinal endoscopy in our hospital seen at the same time as the cases of GC were selected. The exclusion criteria were as follows: *H. pylori*-negative status, history of gastrointestinal surgery, or presence of systemic disease. Ethics approval was obtained from the review board of Dokkyo Medical University, Saitama Medical Center (No. 23036).

H. pylori infection status

The urea breath test (UBT tablets 100 mg; Otsuka Pharmaceutical, Tokyo, Japan) or a stool antigen test (Meridian HpSA ELISA2, Fujirebio, Tokyo, Japan) was also used to confirm eradication of *H. pylori*. If a patient showed negative results for all tests and had a history of eradication, the patient was diagnosed as an *H. pylori*-eradication patient.

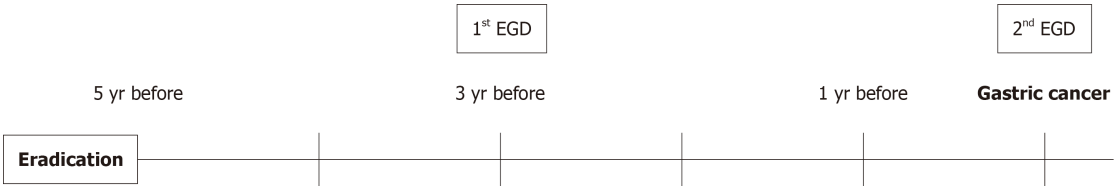

Figure 1 Schematic diagram of the retrospective study design. 1st EGD: First esophagogastroduodenoscopy three years prior to diagnosis of gastric cancer (GC); 2nd EGD: Second esophagogastroduodenoscopy, GC diagnosed at that time.

Endoscopic examination

Endoscopic examinations were performed using Olympus electroscopes (GIF-260H, GIF-290H, GIF-290Z; Olympus, Tokyo, Japan). The Kyoto classification score of GA was evaluated: Atrophy (Kimura-Takemoto classification: C0-CI = A0, CII-CIII = A1, and OI-OIII = A2), intestinal metaplasia (none, IM0; intra-antral, IM1; up to the body, IM2), hypertrophy of gastric folds (negative, H0; positive, H1), nodularity (negative, N0; positive, N1), and diffuse redness (none, DR0; mild, DR1; severe, DR2) (Table 1). The total score was calculated by adding the scores for each parameter. In addition, the atrophy score was calculated and considered in more detail as the modified atrophy score, as C0-C3 (0 to 3) and O1-O3 (4 to 6) (Table 2). Two expert endoscopists assessed and compared the Kyoto classification scores at the time of event onset and three years earlier. Two expert endoscopists reviewed the photographs. In each case, more than 40 endoscopic photographs were taken and reviewed.

Outcome measurement

The outcome was the risk score obtained using the Kyoto classification of changes in gastric mucosa at the time of GC onset and three years earlier.

Statistical analysis

Fisher's exact tests were used for sex comparisons. The Wilcoxon rank-sum test was performed to compare age and risk scores obtained using the Kyoto classification of GA between the GC and GA groups. The modified atrophy score was compared by the Wilcoxon rank-sum test. Changes over time in each of the two groups were examined using the Wilcoxon signed-rank test. A two-sided value of $P < 0.05$ was considered significant. All statistical analyses were performed using the software (SAS Institute, Cary, NC, United States).

RESULTS

Patients' characteristics

Thirty cases of early GC and thirty cases of chronic GA were evaluated. Although no difference in mean age was observed between the two groups, there were significantly more male patients in the GC group. The pathology of the cancer cases was differentiated adenocarcinoma, except for one case of undifferentiated adenocarcinoma, and the depth of invasion was 96% mucosal carcinoma (Table 3).

Overlooked cancers

In the case of GC, the examination findings taken three years before the onset of cancer were evaluated to see if any cancer had been missed, focusing on the area where ESD was performed. No oversights could be confirmed.

Kyoto classification score of all cases at the time of onset of GC and three years earlier

The total score was significantly higher in the GC group both at the time of cancer onset and three years earlier (4.97 *vs* 3.73, $P = 0.0034$; 4.2 *vs* 3.1, $P = 0.0035$, respectively). In terms of changes over time, total scores decreased significantly in both groups (4.97 *vs* 4.2, $P = 0.0003$; 3.73 *vs* 3.1, $P = 0.0007$, respectively) (Figure 2). The atrophy score was higher in the GC group at all time points, and no significant changes over time were observed in either group. The intestinal metaplasia score was higher in the GC group at all time points. There were no changes over time in both groups. There was no difference in hypertrophy of gastric folds and nodularity between the two groups at any time point, and no changes over time were observed in either group. The diffuse redness score was higher in the GC group at all time points and improved significantly over time in both groups (Table 4). The decrease in the total score was thought to be mainly due to the decrease in diffuse redness. Image-enhanced endoscopy was performed in some cases, but not all cases.

Modified atrophy score in all cases at the time of onset of GC and three years earlier

The modified atrophy score was significantly higher in the GC group both at the time of cancer onset and three years earlier (5.3 *vs* 4.93, $P = 0.0319$; 4.93 *vs* 4.63, $P = 0.0038$, respectively), and it was significantly improved only in the GA group (5.3 *vs* 5.3, $P = 0.5$; 3.73 *vs* 3.1, $P = 0.0475$, respectively) (Figure 3).

Table 1 Grading system for the Kyoto classification score

Parameter	Score	
Atrophy	0	C0–CI according to Kimura-Takemoto classification
	1	CII–CIII
	2	OI–OIII
Intestinal metaplasia	0	None
	1	Within the antrum
	2	Up to corpus
Hypertrophy of gastrid folds	0	None
	1	Positive
Nodularity	0	None
	1	Positive
Diffuse redness	0	None
	1	Mild (with RAC)
	2	Severe

The score was evaluated by five parameters, with the total score as the sum of these five parameter scores. RAC: Regular arrangement of collecting venules.

Table 2 Modified atrophy score

Modified atrophy score	Kimura-Takemoto classification
0	C0
1	CI
2	CII
3	CIII
4	OI
5	OII
6	OIII

Table 3 Patients' characteristics

Characteristics	Gastric cancer	Gastritis	*P* value
Number	30	30	
Age (yr ± SD)	75.3	73.9	0.695
Sex (M:F)	21:9	17:13	0.422
Differentiation (tub1-2: Sig-por)	29:1		
Depth (m: Sm)	30:0		

SD: Standard deviation; tub1-2: Well to moderate differentiated adenocarcinoma; sig: Signet ring cell carcinoma; por: Poorly differentiated adenocarcinoma; m: Mucosa; Sm: Submucosa.

DISCUSSION

Although the number of deaths from GC is decreasing, its incidence remains high[13]. *H. pylori* infection is the most important cause of GC, and eradication therapy reduces the risk of GC[14,15]. However, the risk of cancer is not eliminated, and GC may develop after eradication[16]. The factors responsible for cancer development after eradication have not been completely elucidated. In this study, it was found that gastric atrophy did not improve in GC cases after era-

Table 4 Each parameter of the Kyoto classification at the time of onset of gastric cancer and three years before onset of gastric cancer

Parameters	1st EGD	2nd EGD	*P* value	1st EGD	2nd EGD	*P* value	1st EGD	2nd EGD	*P* value
	A			**IM**			**H**		
GC	2	2	1	1.27 ± 0.74	1.27 ± 0.74	1	0.43 ± 0.09	0.50 ± 0.504	0.543
GA	1.9±0.305	1.9±0.305	1	0.8 ± 0.76	0.87 ± 0.78	0.326	0.37 ± 0.09	0.367 ± 0.490	0.184
P value	0.0415	0.0415		0.0192	0.046		0.605	0.281	
	N			**DR**					
GC	0.03 ± 0.183	0.03 ± 0.183	1	1.27 ± 0.83	0.5 ± 0.82	0.0004			
GA	0.03 ± 0.183	0	0.326	0.95 ± 0.17	0.07 ± 0.37	0.0008			
P value	1	0.326		0.017	0.012				

A: Atrophy; IM: Intestinal metaplasia; H: Hypertrophy of gastric folds; N: Nodularity; DR: Diffuse redness; GC: Gastric cancer; GA: Gastritis; 1st EGD: First esophagogastroduodenoscopy three years prior to diagnosis of gastric cancer; 2nd EGD: Second esophagogastroduodenoscopy, gastric cancer diagnosed at that time.

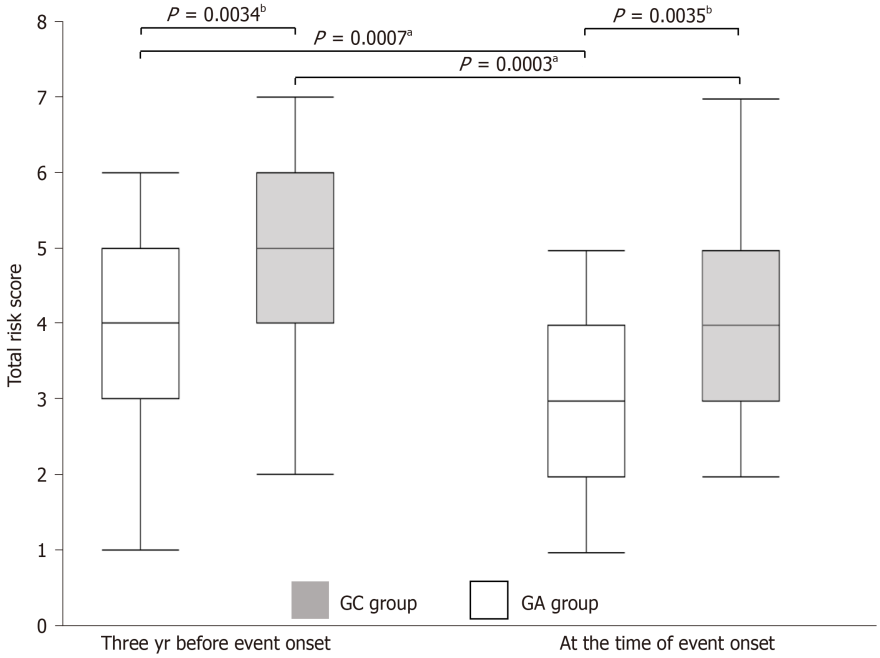

Figure 2 Kyoto classification score at the time of onset of gastric cancer and three years before onset of gastric cancer. Data are medians with interquartile ranges. [a]Wilcoxon signed-rank test; [b]Wilcoxon rank-sum test. GC: Gastric cancer; GA: Gastritis.

dication.

There have been many reports of the relationship between endoscopically diagnosed GA and GC. Therefore, endoscopic diagnosis of GA is very important. Various classifications of GA have been proposed to date. Schindler created the basis for the endoscopic classification of GA[17]. Schindler pointed out the importance of atrophic GA as an origin of GC and stated the importance of follow-up. Later, in Japan, the Kimura-Takemoto classification of atrophic GA was devised [18]. The pathophysiological concept of gastric disease has changed significantly since Warren and Marshall successfully isolated and cultured *H. pylori* in 1983[1]. The classification of GA also changed to take *H. pylori* infection into account, and in 1996, the revised updated Sydney system was created and adopted widely.

The Kyoto classification of GA is based on the previous diagnosis and classification of GA, and it distinguishes among those uninfected, currently infected, and previously infected (including after eradication) with *H. pylori*[19]. The Kyoto classification of GA aims to reflect GC risk. Five elements are included in the endoscopic finding score for GC risk: Atrophy, intestinal metaplasia, diffuse redness, hypertrophy of gastric folds, and nodularity[10].

Sugimoto *et al*[20] reported a comparison of risk scores obtained using the Kyoto classification of GA at the time of GC detection[20]. Scores of GC were significantly higher than GA scores in both non-eradicated and eradicated cases. They identified atrophic GA and intestinal metaplasia as related factors. Shichijo *et al*[21] also reported that atrophy was more involved in the risk score for GC[21]. However, those reports evaluated the risk score obtained using the Kyoto classification of GA at the time of diagnosis of GC. It would be clinically very useful if the Kyoto classification score could be

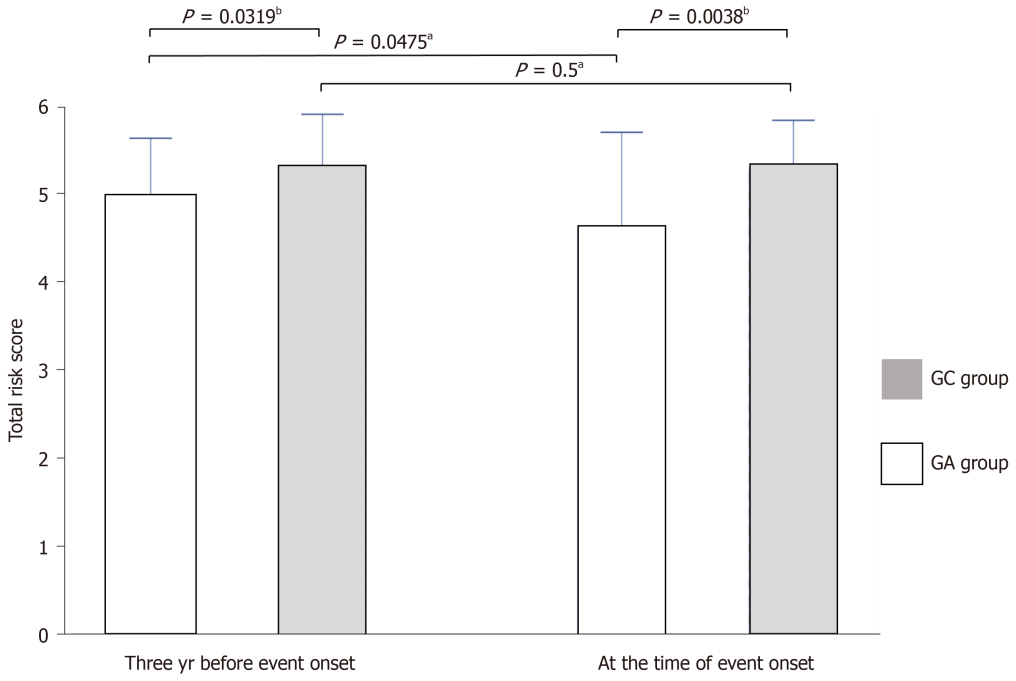

Figure 3 Modified atrophy score at the time of onset of gastric cancer and three years before onset of gastric cancer. [a]Wilcoxon signed-rank test; [b]Wilcoxon rank-sum test. GC: Gastric cancer; GA: Gastritis.

used to show changes in the gastric mucosa after eradication until the onset of gastric cancer. Because it is difficult to conduct a prospective study at a single institution, the present study was a retrospective review.

In the present study, the atrophy score, intestinal metaplasia, diffuse redness, and total score were significantly higher both at initial endoscopy and at the onset of GC after eradication (Table 4). There were no differences in fold enlargement and nodularity between GC cases and GA cases at the time of initial endoscopy or at the time of GC onset. The modified atrophy score was significantly higher both at initial endoscopy and at the onset of GC after eradication. The modified atrophy score did not improve during the course of GC cases after eradication. It is a very important finding that atrophy does not improve in GC cases compared to GA even after eradication. The atrophy score of the Kyoto classification is only 0, 1, or 2, making it difficult to distinguish between the two groups and difficult to interpret the results. In the present study, atrophy was divided into seven categories from 0 to 6.

We previously reported that post-eradication atrophy scores are useful for predicting subsequent cancer[12]. In addition, there are many reports that atrophy scores are high at the time of onset of GC[22]. Atrophic GA is associated with hypermethylation[23]. Aberrant CpG island methylation, particularly in the promoter regions of tumor suppressor genes, is associated with tumorigenesis[24]. Eradication of *H. pylori* has been reported to improve atrophic GA in some cases[3]. Furthermore, improved methylation is reported after eradication[25]. On the other hand, the methylation level of miR-124a-3 was associated with an increased risk of developing metachronous GC[9]. However, it will likely take some time before it can be translated into general clinical practice. In the present cases of GC, these improvements may have been very slow or beyond the so-called point of no return[14,26]. The degree of improvement in the atrophy score is useful for predicting GC after eradication.

All GC in the present study were differentiated adenocarcinomas except for one case, and all were intramucosal carcinomas. Patients with severe atrophy and slow improvement may develop GC after eradication. Even if GC develops after eradication, it can be treated with endoscopy if detected early. Patients at high risk require regular, careful follow-up. The present study included only one case of undifferentiated cancer, so it will be important to evaluate more such cases.

Limitations

This was a single-center, retrospective study with a limited number of cases. In this study, image-enhanced endoscopy was used only for the diagnosis of some cases of intestinal metaplasia. Since endoscopic data at the time of eradication were not available for all cases, endoscopic data from three years before the onset of GC after eradication were used.

CONCLUSION

In conclusion, the results of this retrospective study suggested that the course of the modified atrophy score is useful for predicting the onset of GC after eradication. In particular, patients with severe atrophy even after *H. pylori* eradication should be carefully monitored to detect GC early.

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FOOTNOTES

Author contributions: Suzuki Y, Katayama Y, and Fujimoto Y conceptualized and designed the study, collected data, carried out the initial analysis, and drafted the initial manuscript; Kobori I and Tamano M coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Institutional review board statement: This study was approved by the ethics committee of the Dokkyo Medical University Saitama Medical Center (Approval No. 23036).

Informed consent statement: Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient gave informed consent to treatment. For full disclosure, the details of this retrospective, observational study were published on the home page of the medical center.

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