

ORIGINAL ARTICLE

Predictive value of risk score using Kyoto classification of gastritis a few years prior to diagnosis of early gastric cancer

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Introduction

In 1983, Warren and Marshall succeeded in isolating and culturing *Helicobacter pylori*, and identified this bacterium as a cause of histological gastritis.¹ In gastric mucosa infected by *H. pylori*, the CagA protein produced by *H. pylori* is injected into the gastric mucosa by the type IV secretion system of the bacterium.^{2,3} CagA induces abnormalities in intracellular signal transduction and promotes gastric mucosal inflammation associated with *H. pylori* infection. Gene abnormalities due to persistent inflammation accumulate, leading to gastric carcinogenesis.⁴ Thus, evaluating the risk of gastric cancer according to the state of chronic gastritis is very important. Various classifications of gastritis have been proposed. The Kyoto classification of gastritis is based on past diagnostic classifications of gastritis and adopts simpler, more objective gastritis findings according to *H. pylori* infection status. The Kyoto classification of gastritis was created for the purpose of assessing the risk of individual gastric cancer and unifying the methods of describing gastritis.⁵ Although some studies have examined predictors of gastric cancer,^{6,7} those predictions were mainly based on a single factor. Both studies

Abstract

Background and Aim: Based on past diagnostic classifications of gastritis, the Kyoto classification of gastritis adopts simpler, more objective gastritis findings according to *Helicobacter pylori* infection status and evaluates the risk of gastric cancer. To clarify whether this score can predict future gastric cancer, we retrospectively examined risk scores obtained using the Kyoto classification of gastritis a few years prior to the diagnosis of early gastric cancer.

Methods: We reviewed data from 50 individuals who had undergone upper gastrointestinal endoscopy 2–3 years prior to the diagnosis of early gastric cancer in our hospital. Two expert endoscopists evaluated and compared risk scores obtained using the Kyoto classification of gastritis between cancer and control groups.

Results: With regard to the risk score obtained using the Kyoto classification of gastritis in all cases, atrophy, intestinal metaplasia, diffuse redness, and total score were significantly higher among gastric cancer cases. Among *H. pylori*-eradicated cases, atrophy score was higher in the gastric cancer group. Among patients for whom *H. pylori* had been eradicated for >3 years at first endoscopy, atrophy score was still higher in the gastric cancer group.

Conclusion: This retrospective study suggested that the risk score obtained using the Kyoto classification of gastritis was useful for predicting the onset of gastric cancer. In particular, patients with a high atrophy score even after *H. pylori* eradication may be at high risk of developing gastric cancer.

examined only endoscopic atrophy and concluded that it was a predictor of the development of gastric cancer. The Kyoto classification assesses the risk of gastric cancer using five endoscopic factors.

However, evidence regarding the significance of risk scores obtained using the Kyoto classification of gastritis in terms of gastric cancer risk remains insufficient. Previous studies have focused on risk scores obtained using the Kyoto classification of gastritis at the time gastric cancer was diagnosed. However, consideration of whether this score can predict future gastric cancer development is important. This study retrospectively examined risk scores obtained using the Kyoto classification of gastritis a few years prior to the diagnosis of early gastric cancer and examined whether scores correlated with the development of gastric cancer after a few years compared with control cases.

Methods

Patients and settings. Participants comprised 50 patients who had undergone endoscopic submucosal dissection (ESD) for early gastric cancer in our hospital between 2014 and 2020 and

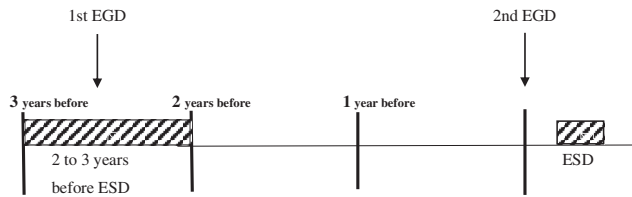


Figure 1 First endoscopy 2–3 years prior to diagnosis of early gastric cancer. EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection.

who had undergone upper gastrointestinal endoscopy 2–3 years prior for diagnosis of early gastric cancer in our hospital (Fig. 1). As controls, we selected from cases of gastritis diagnosed at the same time that had undergone upper gastrointestinal endoscopy in our hospital 2–3 years earlier. Exclusion criteria were as follows: *H. pylori*-negative status, history of gastrointestinal surgery, or presence of systemic disease. Two expert endoscopists evaluated and compared risk scores obtained using the Kyoto classification of gastritis 2–3 years prior to second endoscopy in each group. Furthermore, we examined the risk score according to *H. pylori* infection state. Ethics approval was obtained from the review board at Dokkyo Medical University, Saitama Medical Center.

Endoscopic examination. The risk score obtained using the Kyoto classification of gastritis was evaluated using the following parameters: atrophy, intestinal metaplasia, enlarged folds, nodularity, diffuse redness, and total score (Table 1). The following gastritis parameters were assessed: atrophy (Kimura-Takemoto classification⁸: C0–C1 = A0, CII–CIII = A1, and OI–OIII = A2), intestinal metaplasia (none, IM0; within antrum, IM1; up to the corpus, IM2), enlarged folds (negative, H0; positive, H1), nodularity (negative, N0; positive, N1), and diffuse redness (none, DR0; mild, DR1; severe, DR2). Total score was calculated by adding the scores for each parameter. Two expert

Table 1 Grading system for the Kyoto classification of gastritis

Parameter	Score	
Gastric mucosal atrophy	0	C0–C1 according to Kimura-Takemoto classification
	1	CII–CIII
	2	OI–OIII
Intestinal metaplasia	0	None
	1	Within the antrum
	2	Up to corpus
Enlarged 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.

endoscopists retrospectively examined endoscopic findings 2–3 years prior to the diagnosis of early gastric cancer and calculated the risk score obtained using the Kyoto classification of gastritis. If the two endoscopists provided different scores, the photographs were reviewed, and a consensus agreement was reached. Forty or more endoscopic photographs were taken in each case. Image-enhanced endoscopic photographs were excluded because of differences in the frequency of use.

H. pylori infection status. The infection status of *H. pylori* was evaluated using an anti-*H. pylori* immunoglobulin G serological test (E plate Eiken *H. pylori* antibody; Eiken Chemical Co., Tochigi, Japan) and a rapid urease test (Helicocheck; Otsuka Co., Tokyo, Japan) using two pieces of gastric mucosa. The urea breath test (UBT tablets 100 mg; Otsuka Co.) was also used for confirmation of *H. pylori* eradication. If the patient showed negative results to all tests and had a history of eradication and/or endoscopic atrophic mucosa, the patient was diagnosed as an *H. pylori*-eradicated patient. This study included *H. pylori*-positive and eradicated patients and excluded uninfected patients.

Outcome measurement. The outcome measured was evaluation of the risk score obtained using the Kyoto classification of gastritis a few years prior to diagnosis of early gastric cancer as an index of gastric cancer risk.

Statistical analysis. For comparisons of gender, the chi-squared test was used. The risk score obtained using the Kyoto classification of gastritis was statistically processed as an interval scale because the total score was evaluated after addition. The Wilcoxon rank-sum test was performed to compare age and risk score obtained using the Kyoto classification of gastritis between the two groups. Odds ratios were calculated using logistic regression modeling. A two-sided value of $P < 0.05$ was considered indicative of statistical significance. All statistical analyses were performed using JMP version 12 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. We analyzed 50 cases of early gastric cancer and 50 cases of chronic gastritis. Although no difference in average age was identified between the two groups, significantly more male cases were seen in the gastric cancer group. The pathologies of the cancer cases were all differentiated adenocarcinoma, and the depth of invasion was mucosal carcinoma in 96% (Table 2). Concordance rates of the two endoscopists were 97.1% for atrophy, 87.3% for intestinal metaplasia, 88.2% for enlarged folds, 99.0% for nodularity, and 84.3% for diffuse redness.

Examination of overlooked cancer. In gastric cancer cases, we examined whether any cancers were overlooked, mainly in the areas where ESD was performed. We were unable to confirm any overlooked cases.

Risk score obtained using Kyoto classification of gastritis in total cases. In the risk scores obtained using

Table 2 Characteristics of the total cohort

	Control (endoscopic gastritis)	Case group (early stage gastric cancer)	<i>P</i> value
Number	50	50	
Age (years ± SD)	73.1 ± 6.89	74.6 ± 5.8	0.997
Gender (male: female)	25:25	41:9	0.007
Differentiation: tub1-2/sig-por	—	50/0	
Depth: m/sm	—	48/2	

m, mucosa; por, poorly differentiated adenocarcinoma; sig, signet ring cell carcinoma; sm, submucosa; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma.

Table 3 Risk score obtained using the Kyoto classification of gastritis a few years prior to diagnosis of early gastric cancer

	Control	Case group	<i>P</i> value
Number	50	50	
Atrophy	1.84 ± 0.37	1.98 ± 0.14	0.02
Intestinal metaplasia	0.84 ± 0.77	1.26 ± 0.80	0.01
Enlarged fold	0.40 ± 0.48	0.50 ± 0.51	0.32
Nodularity	0.04 ± 0.10	0.06 ± 0.24	0.65
Diffuse redness	0.94 ± 1.00	1.32 ± 0.89	0.04
Total score	4.00 ± 1.74	5.10 ± 0.58	0.003

the Kyoto classification of gastritis for all cases, atrophy, intestinal metaplasia, diffuse redness, and total score were all significantly higher in gastric cancer cases (Table 3). A logistic analysis of risk factors revealed significant differences in atrophy, intestinal metaplasia, diffuse redness, and total score from univariate analyses. Odds ratios were 9.33 (95% confidence interval [CI], 1.62–176.7), 1.96 (95% CI, 1.18–3.34), and 1.53 (95% CI, 1.01–2.34). No significant differences were identified in multivariate analysis (Table 4). At the time of first endoscopy, *H. pylori*-positive and -negative cases coexisted, so we examined the risk score obtained using the Kyoto classification of gastritis for each *H. pylori* status (Fig. 2).

H. pylori-positive case at first endoscopy. *H. pylori* had not been eradicated at first endoscopy in 21 cases of gastric cancer and 14 cases of gastritis. Risk scores obtained using the Kyoto classification of gastritis did not differ significantly between the two groups (Table 5). In these cases, eradication was usually achieved immediately after endoscopy, making it difficult to evaluate the risk score obtained at least 2–3 years earlier using the Kyoto classification of gastritis for gastric cancer

development. *H. pylori* remained uneradicated in nine cases of gastric cancer and two cases of gastritis until second examination, but these numbers were too small to examine statistically.

H. pylori-negative case at first endoscopy. *H. pylori* had been eradicated at first endoscopy in 29 cases of gastric cancer and 36 cases of gastritis. For risk score obtained using the Kyoto classification of gastritis, atrophy was higher in the gastric cancer group (Table 5). A significant difference in atrophy was also seen among patients for whom *H. pylori* had been eradicated for >3 years at the time of first endoscopy (Table 5). At the time of conducting this study, >5–6 years had passed from the time of *H. pylori* eradication to the onset of cancer.

Discussion

The history of endoscopic gastritis classification starts with Schindler's classification.⁹ In 1972, the Kimura-Takemoto classification, which evaluates the degree of progression of the atrophy border on endoscopy, was published and is still widely used in Japan.⁸ Based on the discovery of the association between *H. pylori* and chronic gastritis in 1984, the Sydney System was advocated in 1990,¹⁰ with an update in 1996.¹¹ In recent years, the Operative Link on Gastritis Assessment (OLGA) classification was proposed to classify the distribution and degree of atrophy in stages.¹² Subsequently, the Operative Link on Gastric Intestinal Metaplasia (OLGIM) classification was advocated to classify the distribution and degree of intestinal metaplasia in the same manner.¹³ As OLGA is a biopsy diagnosis, it can be used for the accurate diagnosis of atrophy and intestinal metaplasia. However, it is an older classification method, and much evidence about its advantages and disadvantages has been accumulated since it was first proposed. In addition, we need to exercise

Table 4 Risk factors for gastric cancer a few years later

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value
Atrophy	9.33	1.62–176.7	0.04	4.16	0.59–84.9	0.22
Intestinal metaplasia	1.96	1.18–3.34	0.01	1.62	0.94–2.86	0.09
Enlarged fold	1.50	0.68–3.34	0.32	1.27	0.54–3.00	0.58
Nodularity	1.00	0.24–12.0	0.65	1.27	0.18–10.9	0.81
Diffuse redness	1.53	1.01–2.34	0.05	1.27	0.80–2.03	0.32

CI, confidence interval; OR, odds ratio.

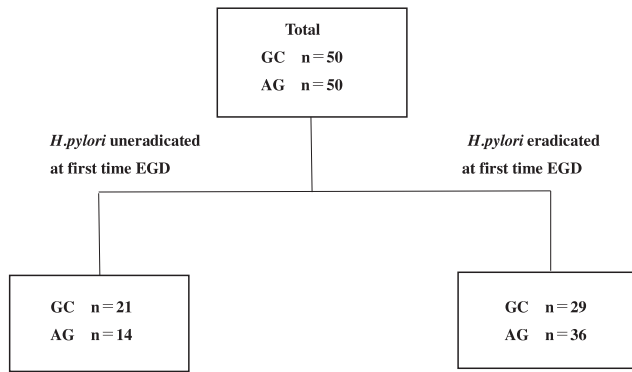


Figure 2 *Helicobacter pylori* infection status at first endoscopy. EGD, esophagogastroduodenoscopy; GA, gastritis; GC, gastric cancer.

caution when performing biopsy on patients receiving anticoagulants.

Based on these established gastritis classifications, the Kyoto classification of gastritis was created with the aim of taking simpler, more objective findings of gastritis according to the *H. pylori* infection status, assessing the risk of individual gastric cancer, and standardizing the description of gastritis.⁵ On the other hand, there is little evidence on the use of the Kyoto classification for the prediction of the risk of gastric cancer. Although the Kyoto classification evaluates the entire stomach, it is associated with the problem of interobserver agreement. However, recently, the use of image-enhanced endoscopes has improved diagnostic ability. Hence, it will be necessary to prospectively evaluate the effects of both classifications on gastric cancer diagnosis in the future.¹⁴ Sugimoto *et al.* compared risk scores obtained using the Kyoto classification of gastritis at the time of gastric cancer detection in 268 cases with scores from 932 cases of gastritis.¹⁵ Scores for gastric cancer were significantly higher than those for gastritis in both uneradicated and eradicated cases. They identified atrophic gastritis and intestinal metaplasia as relevant factors. Multivariate analysis showed a significant difference only for intestinal metaplasia. Shichijo *et al.* also reported that atrophy was more involved in the risk

score for gastric cancer obtained using the Kyoto classification of gastritis.¹⁶

However, those reports evaluated the risk score obtained using the Kyoto classification of gastritis at the time gastric cancer was diagnosed. If the risk score obtained using the Kyoto classification of gastritis can predict the onset of gastric cancer a few years later, this would likely prove clinically very useful. As a prospective study is difficult to conduct in a single center, we performed a retrospective examination. In gastric cancer cases, we examined whether any cancers were overlooked, but we could not confirm any such overlooked cases. Microcancer that could not be visualized by endoscopy could have potentially been present, but we think that the future prediction of the risk score obtained using the Kyoto classification of gastritis at that time is meaningful. In this study, atrophy, intestinal metaplasia, diffuse redness, and total score were significantly higher in gastric cancer cases with regard to the risk score obtained using the Kyoto classification of gastritis at first endoscopy for all cases (Table 3). Severity of gastric mucosal damage correlates with the presence of mutations in the gastric mucosa.^{17,18} In addition, a deep relationship exists between diffuse redness and polymorphonuclear cell infiltration.¹⁹ The excess mucosal production of reactive oxygen metabolites is associated with the equivalent neutrophil infiltration caused by *H. pylori* infection.²⁰ In the logistic analysis of risk factors, atrophy, intestinal metaplasia, diffuse redness, and total score were significantly higher in gastric cancer cases according to univariate analysis. Multivariate analysis showed no significant difference between the groups.

In the examination according to *H. pylori* infection status, 21 cases of gastric cancer and 13 cases of gastritis had not achieved eradication by the time of first endoscopy. No significant difference in score was evident between groups. However, *H. pylori* that is found to be positive on first endoscopy is often later eradicated, so a positive result at the next endoscopy is unlikely. Most of our cases had also undergone eradication after the first endoscopy, so evaluating the score for the development of gastric cancer several years later is difficult. However, among those cases with *H. pylori* eradication after first endoscopy, cases of gastritis showed better improvement in total score at second endoscopy (data not shown). Whether the poor improvement rate of total score after eradication is a cause or result of gastric

Table 5 Risk score obtained using the Kyoto classification of gastritis a few years prior to diagnosis of early gastric cancer according to *Helicobacter pylori* infection status

	Before eradication			After eradication			More than 3 years have passed since eradication at the time of the first endoscopy		
	Control	Case	<i>P</i> value	Control	Case	<i>P</i> value	Control	Case	<i>P</i> value
	14	21		36	29		35	27	
Number	14	21		36	29		35	27	
Atrophy	1.86 ± 0.36	2.00 ± 0.00	0.09	1.78 ± 0.42	1.97 ± 0.03	0.03	1.77 ± 0.43	1.96 ± 0.19	0.04
Intestinal metaplasia	0.79 ± 0.70	1.29 ± 0.85	0.07	0.86 ± 0.80	1.17 ± 0.80	0.13	0.86 ± 0.81	1.22 ± 0.80	0.08
Enlarged fold	0.43 ± 0.51	0.57 ± 0.51	0.43	0.39 ± 0.50	0.45 ± 0.51	0.64	0.40 ± 0.50	0.41 ± 0.50	0.96
Nodularity	0.07 ± 0.27	0.10 ± 0.30	0.84	0.03 ± 0.17	0.03 ± 0.19	0.89	0.03 ± 0.17	0.07 ± 0.27	0.42
Diffuse redness	1.71 ± 0.73	1.71 ± 0.64	0.82	0.64 ± 0.93	0.97 ± 0.94	0.14	0.600.91	1.04 ± 0.94	0.06
Total score	4.86 ± 1.80	5.67 ± 1.20	0.19	3.72 ± 1.63	4.55 ± 1.60	0.06	3.69 ± 1.64	4.67 ± 1.80	0.051

cancer requires further studies to clarify. Consideration of changes in the risk score from the Kyoto classification of gastritis over time is also important.

Among cases with eradicated *H. pylori* at first endoscopy, atrophy score was significantly higher in gastric cancer cases. Atrophy score was significantly higher for gastric cancer patients than for gastritis patients among those in whom *H. pylori* had been eradicated for >3 years at first endoscopy. The association between the development of intestinal metaplasia and gastric cancer is very important.²¹ As it is relatively rare to reach an intestinal metaplasia score of 2 compared to the likelihood of reaching an atrophy score of 2, it was difficult to differentiate between the gastric cancer and gastritis groups. In addition, as mentioned in the Limitations section, this was related to the fact that image-enhanced endoscopy was not used for the diagnosis of intestinal metaplasia.

Take *et al.* also reported that posteradicated atrophic gastritis was associated with gastric cancer.²² Atrophic gastritis is associated with hypermethylation.²³ Aberrant CpG island methylation, especially in promoter regions of tumor suppressor genes, is related to tumorigenesis.²⁴ *H. pylori* eradication may resolve some cases of atrophic gastritis.²⁵ In addition, improvement of methylation has been reported following eradication.²⁶ In cases of gastric cancer, these improvements may be slow or beyond the so-called point of no return.^{27,28} Atrophy score is useful for predicting gastric cancer after eradication with regard to the Kyoto classification of gastritis. All gastric cancers in this study represented differentiated adenocarcinoma and mucosal cancers, except for two cases. Patients with strong atrophy and slow improvement of atrophy after *H. pylori* eradication should be followed carefully, preferably at regular intervals, because they can be treated by ESD even if early cancer develops. As no undifferentiated cancer cases were included in this study, accumulation of such cases is important in the future.

Limitations. This study was a single-center, retrospective study of a limited number of cases. The risk score obtained using the Kyoto classification of gastritis was evaluated by two expert endoscopists, and the concordance rate was lower for diffuse redness than for other parameters. Image-enhanced endoscopy was not used to diagnose intestinal metaplasia in this study. Due to the insufficient number of cases of *H. pylori* eradicated and uneradicated cases, multivariate analysis of each was not possible.

In conclusion, in this retrospective study, the risk score obtained using the Kyoto classification of gastritis was suggested to be useful for predicting the onset of gastric cancer. In particular, the results suggested that patients with a high atrophy score even after *H. pylori* eradication may be at relatively high risk of developing gastric cancer. We need to follow cases of severe atrophy at least once a year.

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