INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Efficacy of the Kyoto Classification of Gastritis in Identifying Patients at High Risk for Gastric Cancer

Mitsushige Sugimoto[1,2], Hiromitsu Ban[1], Hitomi Ichikawa[2], Shu Sahara[2], Taketo Otsuka[3], Osamu Inatomi[3], Shigeki Bamba[3], Takahisa Furuta[4] and Akira Andoh[3]

Abstract

Objective The Kyoto gastritis classification categorizes the endoscopic characteristics of *Helicobacter pylori* (*H. pylori*) infection-associated gastritis and identifies patterns associated with a high risk of gastric cancer. We investigated its efficacy, comparing scores in patients with *H. pylori*-associated gastritis and with gastric cancer.

Methods A total of 1,200 patients with *H. pylori*-positive gastritis alone (n=932), early-stage *H. pylori*-positive gastric cancer (n=189), and successfully treated *H. pylori*-negative cancer (n=79) were endoscopically graded according to the Kyoto gastritis classification for atrophy, intestinal metaplasia, fold hypertrophy, nodularity, and diffuse redness.

Results The prevalence of O-II/O-III-type atrophy according to the Kimura-Takemoto classification in early-stage *H. pylori*-positive gastric cancer and successfully treated *H. pylori*-negative cancer groups was 45.1%, which was significantly higher than in subjects with gastritis alone (12.7%, p<0.001). Kyoto gastritis scores of atrophy and intestinal metaplasia in the *H. pylori*-positive cancer group were significantly higher than in subjects with gastritis alone (all p<0.001). No significant differences were noted in the rates of gastric fold hypertrophy or diffuse redness between the two groups. In a multivariate analysis, the risks for *H. pylori*-positive gastric cancer increased with intestinal metaplasia (odds ratio: 4.453, 95% confidence interval: 3.332-5.950, <0.001) and male sex (1.737, 1.102-2.739, p=0.017).

Conclusion Making an appropriate diagnosis and detecting patients at high risk is crucial for achieving total eradication of gastric cancer. The scores of intestinal metaplasia and atrophy of the scoring system in the Kyoto gastritis classification may thus be useful for detecting these patients.

Key words: *Helicobacter pylori*, gastric cancer, mass screening/MT, risk assessment

(Intern Med 56: 579-586, 2017)
(DOI: 10.2169/internalmedicine.56.7775)

Introduction

Helicobacter pylori, a gram-negative bacterium that can live in the stomach, is a major human pathogen, infecting an estimated 50% of the global population (1), and is associated with peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue lymphoma (MALT) (2). Gastric cancer develops stepwise from an area of chronic *H. pylori* infection, passing through stages of atrophic gastritis, intestinal metaplasia, and dysplasia (3). Severe atrophic gastritis and intestinal metaplasia are well-known risk factors for gastric ulcers as well as gastric cancer (4). Therefore, an accurate risk stratification system for gastric cancer associated with *H. pylori* infection is important for early identification and treatment.

Pathological reporting systems, such as the Sydney system, its Houston-updated version, and the operative link on gastritis assessment (OLGA) system, are widely used to evaluate gastritis severity (5-7). Although pathological evalu-

[1]Division of Digestive Endoscopy, Shiga University of Medical Science Hospital, Japan, [2]First Department of Medicine, Hamamatsu University School of Medicine, Japan, [3]Department of Gastroenterology, Shiga University of Medical Science, Japan and [4]Center for Clinical Research, Hamamatsu University School of Medicine, Japan
Received for publication May 28, 2016; Accepted for publication July 10, 2016
Correspondence to Dr. Mitsushige Sugimoto, sugimo@belle.shiga-med.ac.jp

Table 1. Grading Scores for Kyoto Classification of Gastritis.

Parameter	Score		
Gastric mucosal atrophy	0	None	C0–CI according to Kimura-Takemoto classification
	1	Mild	CII–CIII
	2	severe	OI–OIII
Intestinal metaplasia	0	None	None
	1	Mild	Within the antrum
	2	Severe	Up to the corpus
Hypertrophy of gastric fold	0	Negative	< 5-mm gastric fold width
	1	Positive	≥ 5-mm gastric fold width
Nodularity	0	Negative	None
	1	Positive	Small nodules in the antrum
Diffuse redness	0	Negative	None
	1	Mild	Mild translucency of collecting venules in the body
	2	Severe	Severe translucency of collecting venules in the body

Endoscopic atrophy was assessed by the Kimura-Takemoto classification (15) and classified into six grades: Close (C)-I, C-II, C-III; and Open (O)-I, O-II, and O-III.
The total score was summed from each score of 5 parameters, with a maximum score of 8.

ation using biopsy specimens may be useful for identifying patients at risk for gastric cancer, biopsy confers a risk of gastrointestinal bleeding, especially in patients taking anticoagulants (8). In addition, pathological findings are limited to the information provided by the biopsy specimen itself and cannot provide information about the whole stomach.

The recently developed Kyoto classification of gastritis of endoscopic characteristics of *H. pylori* infection-associated gastritis allows grading of endoscopically-visible risk factors for the development of gastric cancer (9). This classification system divides patients into three groups: *H. pylori*-negative patients (no gastritis), patients with current *H. pylori* infection (active gastritis), and patients previously infected with *H. pylori* (inactive gastritis). The scoring of five parameters of gastritis (atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness; Table 1) should provide an estimate of gastric cancer risk, although the efficacy of the scoring system has not been fully assessed.

In recent years, the Japanese health insurance system has begun to cover *H. pylori* eradication treatment in patients with endoscopically-confirmed *H. pylori*-associated gastritis. A gradual decrease in the severity of atrophy at all sites and intestinal metaplasia in the lesser curvature of the gastric body is generally observed following eradication (10). *H. pylori* eradication therapy has been found to reduce the risk of developing gastric cancer and metachronous gastric cancers after endoscopic resection (11-14).

Although the estimation of gastric cancer risk based on endoscopic findings has previously been attempted by scoring atrophy and intestinal metaplasia (2), whether or not the Kyoto scoring system can effectively identify high-risk patients is unclear. Therefore, to clarify the endoscopic risk factors, we investigated the endoscopic characteristics of gastritis in patients with *H. pylori*-positive gastritis alone and with *H. pylori*-positive and *H. pylori*-negative early-stage gastric cancer and compared their scores.

Materials and Methods

Study protocol

We retrospectively investigated 1,200 cases of known *H. pylori*-positive gastritis without gastric cancer (control group) (n=932), with current *H. pylori* infection plus early-stage gastric cancer (n=189), or with no infection after eradication therapy plus early-stage gastric cancer (n=79) at the University Hospital of Hamamatsu University School of Medicine and the Shiga University of Medical Science Hospital (Table 2). All patients had undergone gastroduodenoscopy and were scored independently according to the Kyoto classification by two expert endoscopists after endoscopy (9). All patients with gastric cancer underwent endoscopic submucosal dissection (ESD) after clinical staging, as described below. We enrolled patients with gastric cancer who underwent ESD from April 2013 to September 2015 at two University Hospitals as well as patients with *H. pylori*-positive gastritis without gastric cancer who attempted to have their *H. pylori* infection eradicated from September 2011 to January 2015 at the University Hospital of Hamamatsu University School of Medicine and from April 2014 to September 2015 at the Shiga University of Medical Science Hospital. Patients with peptic ulcers and without gastric cancer were included in the control group.

The inclusion criteria were age ≥20 years and current or previous *H. pylori* infection. The exclusion criteria were no *H. pylori* infection with no gastric mucosal atrophy, a history of esophageal or stomach surgery, or a significant clinical illness (e.g. advanced cancer, renal failure). Early-stage gastric tumors were clinically diagnosed using endoscopy, endoscopic ultrasonography, histopathology, and computed tomography.

Endoscopy

Gastroduodenal endoscopy was performed, and the findings were independently scored according to the Kyoto clas-

Table 2. Characteristics of Patients Investigated for Gastritis according to the Kyoto Classification of Gastritis.

	Total	Control (endoscopic gastritis alone)	Case group (early-stage gastric cancer)			p value (control vs. case group)	p value (control vs. case group before eradication)	p value (before- vs. after-eradication)
			Total	*H. pylori* uneradicated	*H. pylori* eradicated			
Number	1,200	932	268	189	79			
Age (years ± SD)	60.0±12.6	56.7±11.7	71.3±8.5	71.6±8.6	70.4±8.1	<0.001	<0.001	0.263
Sex (Male:Female)	726:474	526:406	200:68	141:48	59:20	<0.001	<0.001	0.989
Mucosal atrophy: CI,-II/CIII,O-I/ O-II,III	137/774/289	135/639/118	2/145/121	2/106/81	0/39/40	<0.001	<0.001	0.359
Location: Upper/Middle/Low			41/75/152	30/54/105	11/21/47			0.831
Differentiation: tub1-tub2/sig-por			251/17	181/8	70/9			0.028
Depth: m/ sm			250/18	178/11	72/7			0.365
Type: IIa/ IIa+IIc/ IIb/ IIc			119/28/8/115	87/16/5/81	32/10/3/34			0.650

SD: standard deviation, m: mucosa, por, poorly differentiated adenocarcinoma, sig: signet ring cell carcinoma, sm: submucosa, tub1: well-differentiated tubular adenocarcinoma, tub2: moderate-differentiated tubular adenocarcinoma

The tumor locations were divided into the upper (cardia, fornix, and upper third of body), middle (middle/lower body), and lower third (angle and antrum).

sification of gastritis and the Kimura-Takemoto classification by two endoscopists (9, 15). The Kimura-Takemoto gastric atrophy classification scores atrophy as six grades: Closed (C)-I, C-II, C-III, and Open (O)-I, O-II, and O-III (15). In this classification, C-I, C-II, and C-III denote closed-type atrophic patterns, with a margin between the non-atrophic fundic mucosa and atrophic mucosa located in the lesser curvature of the stomach; and O-I, O-II, and O-III denote open-type atrophic patterns, whose margin does not cross the lesser curvature. According to the Kyoto classification of gastritis, patients are classified into three groups based on endoscopic findings: *H. pylori*-negative patients (no gastritis), current *H. pylori*-positive patients (active gastritis), and previous *H. pylori*-infected patients (inactive gastritis). The total score involves five parameters of gastritis, including atrophy (Kimura-Takemoto classification CI = Kyoto A0, CII & C-III = Kyoto A1, and OI-OIII = Kyoto A2), intestinal metaplasia (none: IM0, within antrum: IM1, and up to corpus: IM2), hypertrophy of gastric folds (negative: H0, positive: H1), nodularity (negative: N0, positive: N1), and diffuse redness (negative: DR0, mild: DR1, severe: DR2). These scores were independently calculated for all subjects by two expert endoscopists after endoscopy (Table 1). During endoscopy, more than 40 pictures were taken by an expert endoscopist. When the two endoscopists differed on the score assigned, they arrived at a consensus by reviewing the pictures. The status of intestinal metaplasia was diagnosed using image-enhanced endoscopy, such as narrow band imaging, but not pathological evaluations.

H. pylori status

H. pylori status was evaluated based on the findings from an anti-*Helicobacter pylori* IgG serological test (E plate Eiken *H. pylori* antibody®; Eiken Chemical Co., Ltd., Tochigi, Japan) (cut-off value: 10 U/mL), a rapid urease test (Helicocheck®; Otsuka Co., Tokyo, Japan) using two pieces of gastric mucosa, a polymerase chain reaction analysis for the 23S rRNA gene using gastric juice, and a culture test using two pieces of gastric mucosa. If patients with early-stage gastric cancer had undergone *H. pylori* eradication, their status was evaluated based on the findings from a urea breath test.

We categorized the patients into three groups, as follows: *H. pylori* current infection (with active gastritis), past infection (with inactive gastritis), and never infection (with no gastritis). When results were positive for more than one of any of the detection systems, the patient was diagnosed as positive for *H. pylori* infection (*H. pylori* current infection). When results were negative for all detection systems for *H. pylori* infection and no endoscopic gastric mucosal atrophy was observed, the patient was diagnosed as never *H. pylori* infection. When results were negative for all four detection systems and the patient had an eradication history and/or endoscopic gastric mucosal atrophy, then the patient was diagnosed as having a past infection of *H. pylori*.

Data analysis

The subjects' ages are shown as the mean±standard deviation (SD). The statistical differences in endoscopic parameters between the two groups (gastritis alone and gastric cancer) were assessed via Fisher's exact test. All p values are two-sided, and $p<0.05$ was considered statistically significant. The calculations were conducted using a commercial software program (StatView 5.0®; SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The mean age in the gastric cancer group was significantly higher than in the gastritis control group, irrespective of current *H. pylori* status (Table 2). The proportion of males was higher in the cancer group than in the control group (Table 2). The mean period from *H. pylori* eradication therapy to gastric cancer discovery was 4.6 years, and 72% of the patients had been *H. pylori*-free for less than 5 years before cancer was discovered.

Table 3. ***H. pylori*-associated Gastritis Score according to the Kyoto Classification of Gastritis.**

	Total	Control (endoscopic gastritis alone)	Case group (early-stage gastric cancer)			p value (control vs. case group)	p value (control vs. case group before eradication)	p value (uneradicated vs. eradicated subgroups)
			Total	*H. pylori* uneradicated	*H. pylori* eradicated			
Number	1,200	932	268	189	79			
Atrophy	1.6 ±0.5	1.6±0.6	1.9±0.4	1.9±0.4	1.9±0.3	<0.001	<0.001	0.322
Intestinal metaplasia	0.5±0.7	0.3±0.5	1.1±0.7	1.1±0.7	1.2±0.6	<0.001	<0.001	0.049
Hypertrophy of gastric fold	0.3±0.4	0.3±0.4	0.2±0.4	0.3±0.5	0.1±0.3	0.298	0.426	<0.001
Nodularity	0.1±0.2	0.1±0.2	0.0±0.1	0.0±0.1	0.0±0.0	<0.001	0.003	0.836
Diffuse redness	1.6±0.5	1.6±0.5	1.4±0.7	1.6±0.5	1.0±0.7	<0.001	0.815	<0.001
Total score	4.0±1.1	3.8±1.1	4.6±1.2	4.8±1.1	4.2±1.2	<0.001	<0.001	<0.001

ESD in the cancer group revealed mostly moderate-to-well-differentiated tubular adenocarcinoma (93.7%), with invasion limited to the mucosa (93.3%) (Table 2). In the cancer group, 29.5% of patients (n=79) had undergone previous *H. pylori* eradication treatment. Twenty patients (7.5%) in the uneradicated cancer subgroup had metachronous cancers, as did 16 (20.3%) of the 79 previously eradicated patients. No marked differences were noted in tumor location, tumor depth, or endoscopic type between subjects with or without prior *H. pylori* eradication (Table 2). However, the degree of pathological differentiation significantly differed between these two subgroups, with the prevalence of signet ring cell carcinoma/poorly-differentiated adenocarcinomas significantly higher in the subgroup with previous *H. pylori* eradication (p=0.028) (Table 2).

Kimura-Takemoto classification

The grade of atrophy according to the Kimura-Takemoto classification significantly differed between the control group and the cancer group (p<0.001) or *H. pylori*-positive gastric cancer group (p<0.001) (Table 2). In particular, the rate of OII-OIII type in the cancer group was 45.1%, which was significantly higher than in the control group (12.7%) (p<0.001). No marked differences in atrophy grade were noted between *H. pylori*-uneradicated and eradicated cancer subgroups.

Kyoto classification of gastritis and gastritis score

The concordance rate of the scores for the Kyoto classification between the two expert endoscopists was 92% (94% for gastric mucosal atrophy, 88% for intestinal metaplasia, 96% for enlarged folds, 99% for nodularity, and 83% for diffuse redness).

The grading scores for atrophy, intestinal metaplasia, and total in the cancer group or *H. pylori*-positive gastric cancer group were significantly higher than in the control group (Table 3), while the scores of nodularity and diffuse redness were significantly lower (both p<0.001). The mean total gastritis score in the cancer group was 4.6±1.2, which was significantly higher than in the control group (3.8±1.1; p< 0.001) (Table 3).

Within the cancer subgroups, although no marked differences in the scores of nodularity and atrophy were noted, the scores of diffuse redness and hypertrophy of the gastric folds in the *H. pylori*-uneradicated subgroup were significantly higher than in the eradicated subgroup (Table 3). The mean total score in the *H. pylori*-uneradicated subgroup was 4.8±1.1, which was significantly higher than that in the eradicated subgroup (4.2±1.2; p<0.001) (Table 3).

Kyoto classification of gastritis and metachronous cancer

No significant differences in findings were found between *de novo* cancers and metachronous cancers in any patients, but the differences in the tumor location were significant (Table 4). The scores of diffuse redness in *de novo* cancers were significantly higher than in metachronous cancers, but no marked differences were noted in atrophy, intestinal metaplasia, fold hypertrophy, or nodularity. In patients with eradicated *H. pylori* or non-eradicated *H. pylori*, no significant differences in the background or grading scores according to Kyoto classification of gastritis were noted between *de novo* and metachronous cancers (Table 4).

Univariate and multivariate analyses for development of gastric cancer

The results of a univariate analysis revealed the risk factors for gastric cancer to be atrophy and intestinal metaplasia (Table 5). Nodularity and diffuse redness seemed to confer protection. Among the patients that were over 65 years of age, the risk significantly increased in the presence of atrophy (odds ratio (OR): 2.813, 95% confidence interval (CI): 1.817-4.356) and intestinal metaplasia (6.303, 4.440-8.950) (Table 5). Diffuse redness was again protective. When compared with the risk of gastric cancer in comparison with *H. pylori*-positive gastric cancer patients before eradication therapy and gastritis, the risk factors for gastric cancer were identified to be atrophy and intestinal metaplasia (Table 5). Among patients over 65 years of age, the risk significantly increased in the presence of atrophy (OR: 2.522, 95% CI: 1.570-4.050) and intestinal metaplasia (5.294, 3.694-7.587) (Table 5).

In a multivariate analysis of all of the patients, the risk factors were intestinal metaplasia (OR: 4.970, 95% CI:

Table 4. Findings of Patients with Gastric Cancer according to the Kyoto Classification of Gastritis.

	Total		p value	After eradication		p value	Before eradication		p value
	First time	Metachronous		First time	Metachronous		First time	Metachronous	
Number	248	20		63	16		185	4	
Age (years ± SD)	72.1±8.5	71.8±8.5	0.791	70.4±8.1	70.3±8.5	0.844	71.5±8.6	77.5±6.5	0.169
Sex (Male:Female)	183:65	17:3	0.268	44:19	15:1	0.050	139:46	2:2	0.253
Mucosal atrophy: CI,-II/CIII,O-I/ O-II,III	2/134/112	0/11/9	0.921	0/31/32	0/8/8	0.875	2/103/80	0/3/1	0.738
Location: Upper/Middle/Low	38/71/139	3/4/13	0.002	9/17/37	2/4/10	0.961	29/54/102	1/0/3	0.436
Differentiation: tub1-tub2/sig-por	234/14	17/3	0.099	57/6	13/3	0.209	177/8	4/0	0.670
Depth: m/ sm	230/18	20/0	0.216	56/7	16/0	0.163	174/11	4/0	0.615
Type: IIa/IIa+IIc/IIb/IIc	113/24/8/103	6/2/0/12	0.273	28/8/3/24	4/2/0/10	0.293	85/16/5/79	2/0/0/2	0.915
Time from eradication (months)				45.7±33.9	62.2±29.8	0.193			
Kyoto classification									
Atrophy	1.9±0.4	1.9±0.4	0.837	1.9±0.3	1.9±0.3	0.714	1.9±0.3	1.8±0.5	0.580
Intestinal metaplasia	1.1±0.7	1.3±0.6	0.356	1.3±0.7	1.3±0.6	0.604	1.1±0.8	1.0±0.8	0.885
Hypertrophy of gastric fold	0.2±0.4	0.1±0.3	0.149	0.1±0.3	0.1±0.3	0.697	0.3±0.5	0.3±0.3	0.856
Nodularity	0.0±0.1	0.0±0.0	0.688	0.0±0.0	0.0±0.0	0.937	0.0±0.1	0.0±0.0	0.836
Diffuse reddness	1.5±0.6	1.1±0.8	0.015	1.0±0.6	1.0±0.8	0.884	1.6±0.5	1.5±0.6	0.633
Total score	4.7±1.2	4.3±1.4	0.120	4.2±1.1	4.2±1.5	0.909	4.8±1.1	4.5±1.3	0.566

SD: standard deviation, NA: no data available

Endoscopic atrophy was assessed by the Kimura-Takemoto classification (15) and classified into six grades: Close (C)-I, C-II, C-III; and Open (O)-I, O-II, and O-III. The tumor locations were divided into three locations, upper (cardia, fornix, and upper third of body), middle (middle and lower body), and lower third (angle and antrum). "*De novo*" is the first gastric cancer of a patient's life, and "metachronous" is a new second gastric cancer arising within one year of endoscopic resection of the first.

Table 5. Risk Factors for *H. pylori*-positive Gastric Cancer before Eradication Therapy in a Univariate Analysis.

Factor	All patients			Over 65 years old (n =208)			*H. pylori* positive patients: gastritis vs. gastric cancer before eradication			*H. pylori* positive patients: gastritis vs. gastric cancer before eradication: Over 65 years old		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Atrophy	4.228	2.935-6.091	<0.001	2.813	1.817-4.356	<0.001	3.791	2.516-5.714	<0.001	2.522	1.570-4.050	0.001
Intestinal metaplasia	5.761	4.602-7.212	<0.001	6.303	4.440-8.950	<0.001	4.949	3.902-6.278	<0.001	5.294	3.694-7.587	<0.001
Hypertrophy of gastric fold	0.844	0.613-1.161	0.297	0.951	0.621-1.457	0.818	1.151	0.814-1.627	0.426	1.297	0.830-2.028	0.254
Nodularity	0.109	0.027-0.450	0.002	0.774	0.108-5.544	0.799	0.155	0.038-0.642	0.010	1.102	0.154-7.900	0.923
Diffuse reddness	0.566	0.445-0.721	<0.001	0.722	0.530-0.985	0.040	1.038	0.761-1.415	0.815	1.305	0.892-1.910	0.170

CI: confidence interval

Table 6. Risk Factors for *H. pylori*-positive Gastric Cancer before Eradication Therapy in a Multivariate Analysis.

Factor	All patients			Over 65 years old (n =208)			*H. pylori* positive patients: gastritis vs. gastric cancer before eradication			*H. pylori* positive patients: gastritis vs. gastric cancer before eradication: Over 65 years old		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Age	1.144	1.118-1.169	<0.001	0.988	0.958-1.018	0.429	1.158	1.128-1.188	<0.001	1.000	0.966-1.035	1.000
Sex	1.871	1.240-2.824	0.003	1.659	1.027-2.681	0.039	1.737	1.102-2.739	0.017	1.693	1.009-2.841	0.046
Atrophy	1.420	0.898-2.243	0.133	1.822	1.087-3.056	0.023	1.429	0.863-2.366	0.166	1.617	0.936-2.796	0.085
Intestinal metaplasia	4.970	3.798-6.502	<0.001	5.954	4.157-8.527	<0.001	4.453	3.332-5.950	<0.001	5.215	3.604-7.548	<0.001
Hypertrophy of gastric fold	0.872	0.560-1.359	0.872	1.096	0.643-1.866	0.737	1.081	0.676-1.729	0.746	1.286	0.743-2.224	0.369
Nodularity	0.538	0.083-3.481	0.538	0.459	0.011-18.680	0.680	1.022	0.180-5.860	0.980	0.746	0.042-13.218	0.842
Diffuse reddness	0.726	0.520-1.015	0.726	0.869	0.596-1.267	0.466	0.869	0.970-2.257	0.686	1.600	1.009-2.538	0.046

CI: confidence interval, OR: odds ratio

3.798-6.502), age, and male sex (Table 6). Of patients over 65 years of age, the risk for gastric cancer significantly increased in the presence of intestinal metaplasia (OR: 5.954, 95% CI: 4.154-8.527), atrophy (1.822, 1.087-3.056), and male sex (1.659, 1.027-2.681). Atrophy, male sex, and intestinal metaplasia were therefore deemed risk factors in patients over 65 years of age. In a multivariate analysis of all patients, when comparing the risks between *H. pylori*-positive gastric cancer patients and gastritis, the risk factors were found to be intestinal metaplasia (OR: 4.453, 95% CI: 3.332-5.950), age, and male sex (Table 6).

Discussion

The identification of *H. pylori*-positive patients at an increased risk of developing gastric cancer is important. At present, however, although possible factors such as pro-inflammatory cytokines (e.g. interleukin-1beta and tumor necrosis factor-alpha) (16, 17), prostate stem cell antigen gene (18), methylation levels of any genes (e.g. miR-124a-3, empty spiracles homeobox 1 [EMX1] and NK6 homeobox 1 [NKX6-1]) (19), and *H. pylori* virulent factors (e.g. *cagA* and *vacA*) (20, 21) have been cited, their relationship with risk has not been fully characterized. Although the presence

of atrophy and intestinal metaplasia has been widely recognized as a carcinogenic background, a simple and safe method of identifying patients at increased risk is necessary. Here, we demonstrated the efficacy of the scores of intestinal metaplasia and atrophy of a scoring system in the Kyoto classification of gastritis for endoscopic detection of patients at high risk of developing gastric cancer. Increased risk for gastric cancer was found to be associated with endoscopic intestinal metaplasia, higher age, and male sex. In patients over 65 years of age, intestinal metaplasia conferred the highest risk. Patients infected with *H. pylori* require frequent endoscopic follow-up, and the Kyoto classification system, especially its scores of intestinal metaplasia and atrophy, lends itself to rapid identification of those at high risk.

Kyoto classification of gastritis

The extent of atrophy accompanied by intestinal metaplasia confer an increased current and future risk for developing differentiated gastric cancer (2, 12, 22). The cancer rate in relation to the degree of atrophy is 0% for C-I type, 0.25% for C-II, 0.71% for C-III, 1.32% for O-I, 3.70% for O-II, and 5.33% for O-III, according to the Kimura-Takemoto classification, showing a significant increase in the detection rate as atrophy progresses (23). The risk of developing gastric cancer after *H. pylori* eradication therapy increases with the severity of atrophy (13). The Kyoto classification of gastritis tries to grade a risk of gastric cancer using five parameters associated with *H. pylori* infection, not only the atrophy score alone.

In the present study, because we enrolled patients with early-stage gastric cancer, the lesion characteristics of the cancer group were mostly well- to moderately-differentiated adenocarcinoma (93.7%), and pathological depth of tumor invasion (93.3%) was generally confined to the mucosa. Although the small number of diffuse-type gastric cancers and advanced-stage cancers may have biased the estimation of gastric cancer risk, we demonstrated that, in patients over 65 years of age, the risk of gastric cancer significantly increases in the presence of intestinal metaplasia (OR: 5.954, 95% CI: 4.154-8.527), atrophy (1.822, 1.087-3.056), and male sex (1.659, 1.027-2.681). These results support previous reports showing that the rate of gastric carcinogenesis increases with the progression of atrophy and intestinal metaplasia with age. In addition, the total score of this grading system is useful in selecting patients at an increased risk of gastric cancer.

In this study, the scores of diffuse redness in *de novo* cancers were significantly higher than in metachronous cancers, but no marked differences were noted in atrophy, intestinal metaplasia, fold hypertrophy, or nodularity. In general, a score of diffuse redness suggests current *H. pylori* infection. In this study, the prevalence of current *H. pylori* infection was 74.6% (185/248) in cancer developed at first-time and 20.0% (4/20) in metachronous cancer. Because the Japanese health insurance system covers eradication therapy for patients after endoscopic treatment of early gastric cancer, most cases with gastric cancer developed *de novo* had had their infection eradicated. Therefore, the diffuse redness score was lower in the metachronous gastric cancer group than in the gastric cancer group developed *de novo*, due to differences in the infection rate of *H. pylori*. Our hypothesis was supported by the fact that, in patients with eradicated *H. pylori*, no significant differences in the background or grading scores according to the Kyoto classification of gastritis were revealed between *de novo* and metachronous cancers.

In this study, we enrolled patients with early-stage gastric cancer, mostly well differentiated-type adenocarcinoma. Therefore, it is unclear whether intestinal metaplasia, atrophy, enlarged folds, nodularity, and diffuse redness are useful for identifying higher risk groups of diffuse type and/or advanced-stage adenocarcinoma. Future studies should re-evaluate the efficacy of this system for patients with diffuse type and/or advanced-stage adenocarcinoma.

Nodularity and gastric cancer

Recently, screening endoscopy in Japanese young adults, especially women, has revealed a possible association between nodular gastritis and increased risk of undifferentiated-type gastric cancer (24, 25). In the present study, no patient treated for gastric cancer by ESD had nodularity, suggesting that the cancer risk from nodularity is lower in elderly and male patients with intestinal-type gastric cancer than in younger individuals and women. However, further studies will be needed to clarify whether or not the Kyoto classification of gastritis score for nodularity is useful in effectively identifying groups at increased risk for gastric cancer.

Eradication therapy and Kyoto classification of gastritis

Eradication of *H. pylori* is expected to decrease the gastric cancer risk and reduce mortality by removing the reservoir of *H. pylori* infection (2, 11, 26, 27). In a meta-analysis of randomized controlled trials using *H. pylori*-positive healthy asymptomatic individuals, the relative risk for developing gastric cancer with eradication therapy compared with placebo or no treatment was 0.66 (28). In addition, eradication therapy significantly reduced the risk of developing metachronous gastric cancer after endoscopic resection of early-stage gastric cancer (2, 11, 27). In patients followed up for a mean of 5.6 years after eradication, gastric cancer developed in 1.67%, conferring a risk of 0.30% per year (13). In a meta-analysis, *H. pylori* eradication prevented the development of metachronous gastric cancers after endoscopic resection (29). After eradication therapy, the total score of this grading system decreased due to improvement of diffuse redness and hypertrophy of gastric folds. As such, when this grading system is applied to patients after eradication, physicians should pay attention to the lower threshold for abnormalities in the total score. A different grading system may be required to determine risk in patients with and without *H. pylori* infection eradication.

Limitations

The time elapsed after eradication therapy is important when evaluating the scores of the Kyoto classification, because the scores are expect to decrease with time after eradication therapy. Therefore, although we should compare the gastritis scores before and after eradication, because more than 75% of patients were introduced from other hospitals/clinics for endoscopic gastric cancer resection, it is hard to compare these values. Therefore, future studies will need to compare the gastritis scores between before and after eradication as a prospective study.

Conclusion

In conclusion, we demonstrated that the scores of intestinal metaplasia and atrophy of the Kyoto classification scoring system for gastritis proved clinically useful for identifying patients at elevated risk for early-stage gastric cancer, irrespective of *H. pylori* infection. If possible, eradication should be conducted prior to the development of atrophy and intestinal metaplasia to achieve a gastric cancer-preventing effect. A follow-up system might combine Kyoto endoscopic staging and pathological evaluation, such as the Sydney system, its Houston-updated version, and the OLGA system (5-7). The results should be confirmed by future investigations for patients with diffuse type and/or advanced-stage adenocarcinoma using a multicenter prospective design.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

This study was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (15K08948).

References

1. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection--the Maastricht IV/ Florence Consensus Report. Gut **61**: 646-664, 2012.
2. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med **345**: 784-789, 2001.
3. Correa P, Haenszel W, Cuello C, et al. A model for gastric cancer epidemiology. Lancet **2**: 58-60, 1975.
4. Graham DY. *Helicobacter pylori* infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. Gastroenterology **113**: 1983-1991, 1997.
5. Dixon MF, Genta RM, Yardley JH, et al. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol **20**: 1161-1181, 1996.
6. Rugge M, Correa P, Di Mario F, et al. OLGA staging for gastritis: a tutorial. Dig Liver Dis **40**: 650-658, 2008.
7. Rugge M, Meggio A, Pennelli G, et al. Gastritis staging in clinical practice: the OLGA staging system. Gut **56**: 631-636, 2007.
8. Iwatsuka K, Gotoda T, Kusano C, et al. Clinical management of esophagogastroduodenoscopy by clinicians under the former guidelines of the Japan Gastroenterological Endoscopy Society for patients taking anticoagulant and antiplatelet medications. Gastric Cancer **17**: 680-685, 2014.
9. Kamada T, Haruma K, Inoue K, et al. *Helicobacter pylori* infection and endoscopic gastritis -Kyoto classification of gastritis. Nihon Shokakibyo Gakkai Zasshi **112**: 982-993, 2015 (in Japanese).
10. Kodama M, Murakami K, Okimoto T, et al. Ten-year prospective follow-up of histological changes at five points on the gastric mucosa as recommended by the updated Sydney system after *Helicobacter pylori* eradication. J Gastroenterol **47**: 394-403, 2012.
11. Fukase K, Kato M, Kikuchi S, et al. 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 **372**: 392-397, 2008.
12. Take S, Mizuno M, Ishiki K, et al. The effect of eradicating *Helicobacter pylori* on the development of gastric cancer in patients with peptic ulcer disease. Am J Gastroenterol **100**: 1037-1042, 2005.
13. Take S, Mizuno M, Ishiki K, et al. The long-term risk of gastric cancer after the successful eradication of *Helicobacter pylori*. J Gastroenterol **46**: 318-324, 2011.
14. Li WQ, Ma JL, Zhang L, et al. Effects of *Helicobacter pylori* treatment on gastric cancer incidence and mortality in subgroups. J Natl Cancer Inst, in press.
15. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy **1**: 87-97, 1969.
16. Sugimoto M, Furuta T, Shirai N, et al. Different effects of polymorphisms of tumor necrosis factor-alpha and interleukin-1 beta on development of peptic ulcer and gastric cancer. J Gastroenterol Hepatol **22**: 51-59, 2007.
17. El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature **404**: 398-402, 2000.
18. Ichikawa H, Sugimoto M, Uotani T, et al. Influence of prostate stem cell antigen gene polymorphisms on susceptibility to *Helicobacter pylori*-associated diseases: a case-control study. Helicobacter **20**: 106-113, 2015.
19. Asada K, Nakajima T, Shimazu T, et al. Demonstration of the usefulness of epigenetic cancer risk prediction by a multicentre prospective cohort study. Gut **64**: 388-396, 2015.
20. Sugimoto M, Yamaoka Y. Virulence factor genotypes of *Helicobacter pylori* affect cure rates of eradication therapy. Arch Immunol Ther Exp (Warsz) **57**: 45-56, 2009.
21. Yamaoka Y, Kita M, Kodama T, et al. *Helicobacter pylori* cagA gene and expression of cytokine messenger RNA in gastric mucosa. Gastroenterology **110**: 1744-1752, 1996.
22. Imai T, Kubo T, Watanabe H. Chronic gastritis in Japanese with reference to high incidence of gastric carcinoma. J Natl Cancer Inst **47**: 179-195, 1971.
23. Masuyama H, Yoshitake N, Sasai T, et al. Relationship between the degree of endoscopic atrophy of the gastric mucosa and carcinogenic risk. Digestion **91**: 30-36, 2015.
24. Shiotani A, Uedo N, Iishi H, et al. Predictive factors for metachronous gastric cancer in high-risk patients after successful *Helicobacter pylori* eradication. Digestion **78**: 113-119, 2008.
25. Miyamoto M, Haruma K, Yoshihara M, et al. Five cases of nodular gastritis and gastric cancer: a possible association between nodular gastritis and gastric cancer. Dig Liver Dis **34**: 819-820, 2002.
26. Graham DY, Shiotani A. The time to eradicate gastric cancer is now. Gut **54**: 735-738, 2005.
27. Uemura N, Mukai T, Okamoto S, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev **6**: 639-642, 1997.
28. Ford AC, Forman D, Hunt RH, et al. *Helicobacter pylori* eradica-

tion therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ **348**: g3174, 2014.

29. Yoon SB, Park JM, Lim CH, et al. Effect of *Helicobacter pylori* eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter **19**: 243-248, 2014.