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【 ORIGINAL ARTICLE 】

Gastric Xanthoma Is a Predictive Marker for Early Gastric Cancer Detected after *Helicobacter pylori* Eradication

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Abstract:

Objective The detection of early gastric cancer (GC) after *Helicobacter pylori* eradication is expected to increase in Japan. However, the predictive markers for early GC detected after *H. pylori* eradication have not been extensively studied. We conducted a retrospective, single-center observational study to investigate the predictive markers for early GC detected after *H. pylori* eradiation.

Methods A total of 421 patients underwent endoscopic submucosal dissection for early GC at NTT West Osaka Hospital between June 2006 and August 2017. Data from patients with GC (Group C; n=70) and without GC (Group NC; n=114) after *H. pylori* eradication were analyzed.

Results The proportion of men was significantly higher in Group C than in Group NC (92.9% vs. 65.8%; p <0.0001). Complications with other malignant diseases were more prevalent in Group C than in Group NC. A significantly greater proportion of patients had gastric xanthoma (GX) in Group C than in Group NC (64.3% vs. 14.9%; p<0.0001). Regarding scores for endoscopic findings related to the risk of GC, the atrophy score, intestinal metaplasia score and total score were significantly higher in Group C than in Group NC. A multivariate logistic regression analysis identified male sex, atrophy (open type), the presence of intestinal metaplasia and GX as independent predictors for early GC detected after *H. pylori* eradication. An atrophy-matched control analysis also identified GX as an independent predictor.

Conclusion GX is a novel predictive marker for early GC detected after *H. pylori* eradication.

Key words: endoscopic score, gastric cancer, gastric xanthoma, *Helicobacter pylori*, predictive marker

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Introduction

Gastric cancer (GC) is one of the most common causes of cancer death worldwide (1, 2). Many studies have reported that successful *Helicobacter pylori* eradication helps prevent GC development (3-6). In 2013, *H. pylori* eradication for chronic gastritis achieved world-first coverage under the Japanese national health insurance system. Surveillance esophagogastroduodenoscopy (EGD) is also performed after *H. pylori* eradication. As such, the rate of detection of early GC after *H. pylori* eradication is expected to increase in Japan. However, predictive markers for early GC detected after *H. pylori* eradication have not been sufficiently studied.

Previous studies (3, 7-10) have designated atrophy, intestinal metaplasia, fold enlargement, nodularity and diffuse redness as predictive markers; in addition, the scores for endoscopic findings related to the risk of GC were published in the Kyoto global consensus report on *H. pylori* gastritis (11, 12). Furthermore, the presence of gastric xanthoma (GX) was reported to be a predictive marker for early GC (13-16). However, the effectiveness of these scores and GX as predictive markers for early GC detected after *H. pylori* eradication remains unknown.

The present study aimed to investigate predictive markers for early GC detected after *H. pylori* eradication, including scores for endoscopic findings related to the risk of GC and the presence of GX.

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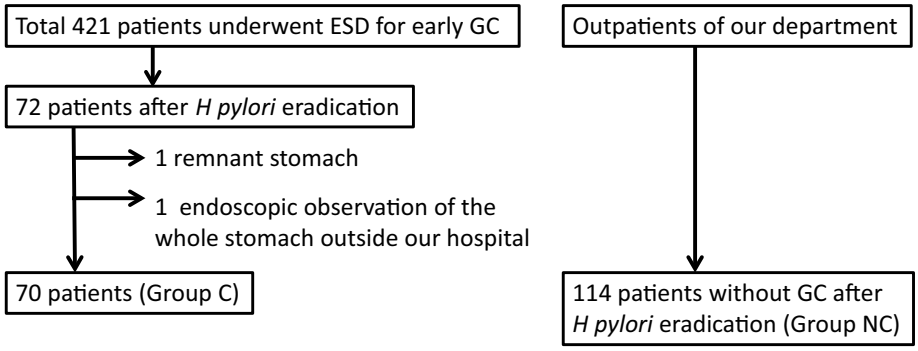

Figure. **Flow chart of the study patients. GC: gastric cancer**

Materials and Methods

Patients

A total of 421 patients underwent endoscopic submucosal dissection (ESD) for early GC at NTT West Osaka Hospital (Osaka, Japan) between June 2006 and August 2017. Of these, 72 patients developed early GC detected after *H. pylori* eradication. Exclusion criteria included remnant stomach and endoscopic observation of the whole stomach outside of our hospital. Ultimately, 184 patients, including 70 patients with GC (Group C) and 114 outpatients of our department without GC (Group NC) after *H. pylori* eradication, were enrolled. Regarding Group NC, patients visiting our department as of August 2017 were enrolled (Figure). The ^{13}C urea breath test or stool antigen test was used to confirm the successful eradication of *H. pylori*. The following variables were investigated: sex, age, complications with other malignant disease (past history or during treatment)/diabetes mellitus, endoscopic characteristics, and scores for endoscopic findings related to the risk of GC. Endoscopic images were reviewed by one expert endoscopist. Endoscopic images of Group C patients were reviewed at the time of ESD or the GC diagnosis. Endoscopic images of Group NC patients were evaluated at the final EGD procedure. Follow-up durations of Group C means durations between *H. pylori* eradication to GC diagnosis.

The severity of gastric atrophy was classified according to the criteria of Kimura and Takemoto (17). GX was diagnosed by the presence of yellowish-white slightly elevated or flat lesions on white-light imaging. Scores for endoscopic findings related to the risk of GC were calculated as follows: 1) atrophy: 0 for C-0 and C-1, 1 for C-2 and C-3, 2 for O-1, 2, 3, and P; 2) intestinal metaplasia: 0 for absence, 1 for presence at gastric antrum, 2 for presence at gastric antrum and corpus; 3) fold enlargement: 0 for absence, 1 for presence; 4) nodularity: 0 for absence, 1 for presence; and 5) diffuse redness: 0 for none, 1 for minor, 2 for severe. Regarding atrophy, O-P was the state in which gastric atrophy had progressed to the whole stomach. Intestinal metaplasia was confirmed by the presence of a grayish-white flat elevated lesion or map-like redness on white-light imaging.

This study was carried out with the approval of the Ethics Committee of NTT West Osaka Hospital (Osaka, Japan). Research was conducted in accordance with the Declaration of Helsinki. Due to the anonymous nature of the data obtained after each patient had provided their written informed consent for ESD and EGD, the requirement for informed consent for this study was waived.

Statistical analyses

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (18). We used Fisher's exact test to compare the relationships between the groups. We used the Mann-Whitney *U* test to investigate the differences between the groups when the data were not parametric. A multivariate logistic regression analysis was used to identify predictive markers for early GC detected after *H. pylori* eradication. For the atrophy-matched control analysis, the Mantel-Haenszel test and conditional logistic regression analysis were used. Variables with $p<0.1$ in the univariate analysis were included in the multivariate analysis. The threshold for significance was $p<0.05$.

Results

Baseline characteristics

The baseline characteristics of the two groups are summarized in Table 1. Group C patients were significantly older than Group NC patients. The proportion of men was significantly higher in Group C than in Group NC (92.9% vs. 65.8%; $p<0.0001$). Complications with other malignant diseases were more prevalent in Group C than in Group NC (47.1% vs. 21.1%; $p=0.0003$). The mean follow-up durations of Group C and Group NC after *H. pylori* eradication were 5.0±3.4 and 5.4±5.1 years, respectively ($p=0.3$).

Endoscopic characteristics

The endoscopic characteristics are summarized in Table 2. The proportions of patients with atrophy (open type) (90.0% vs. 61.4%; $p<0.0001$), intestinal metaplasia (90.0% vs. 49.1%; $p<0.0001$), and GX (64.3% vs. 14.9%; $p<0.0001$)

Table 1. Baseline Characteristics of the Two Groups.

Characteristic	Group C (n=70)	Group NC (n=114)	p value
Age, median [IQR], years	70 [64-75]	66 [60-72.75]	0.007
Male sex, n (%)	65 (92.9)	75 (65.8)	<0.0001
DM, n (%)	19 (27.1)	21 (18.4)	0.2
Other malignant disease, n (%)	33 (47.1)	24 (21.1)	0.0003

DM: diabetes mellitus, IQR: interquartile range

Table 2. Endoscopic Characteristics of the Two Groups.

Characteristic	Group C (n=70)	Group NC (n=114)	p value
Atrophy (open type), n (%)	63 (90.0)	70 (61.4)	<0.0001
Intestinal metaplasia, n (%)	63 (90.0)	56 (49.1)	<0.0001
GX, n (%)	45 (64.3)	17 (14.9)	<0.0001

GX: gastric xanthoma

Table 3. Scores for Endoscopic Findings Related to the Risk of Gastric Cancer in the Two Groups.

	Group C (n=70)	Group NC (n=114)	p value
Atrophy			<0.0001
0	0	0	
1	7	45	
2	63	69	
Intestinal metaplasia			<0.0001
0	7	58	
1	38	45	
2	25	11	
Fold enlargement			0.5
0	70	112	
1	0	2	
Nodularity			1
0	70	114	
1	0	0	
Diffuse redness			0.2
0	0	0	
1	62	107	
2	8	7	
Total score, median [IQR]	4 [4-5]	3 [3-4]	<0.0001

IQR: interquartile range

were significantly higher in Group C.

Scores for endoscopic findings related to the risk of GC

Scores for endoscopic findings related to the risk of GC are shown in Table 3. The atrophy, intestinal metaplasia, and total scores were significantly higher for Group C than for Group NC (p<0.0001). Nodularity was absent in all patients.

The multivariate logistic regression analysis

Age, male sex, complications with other malignant diseases, atrophy (open type), the presence of intestinal metaplasia and GX were included in the multivariate logistic regression analysis. The total score was excluded due to the strong association between atrophy and intestinal metaplasia. Male sex, atrophy (open type), the presence of intestinal metaplasia and GX were confirmed as independent predictors for GC detected after *H. pylori* eradication (Table 4).

The atrophy-matched control analysis

Atrophy was significantly associated with GX (p<0.0001). To clarify the value of GX as the predictive marker of early GC detected after *H. pylori* eradication, atrophy-matched control analysis was performed. A total of 70 patients in Group C and 70 atrophy-matched controls in Group NC were examined. The clinical features of the two groups are

Table 4. Multivariate Analysis of Predictive Markers for Gastric Cancer Detected after *Helicobacter Pylori* Eradication.

Variable	OR	p value
Age	1.04 (0.99-1.09)	0.09
Male sex	7.42 (2.26-24.3)	0.0009
Other malignant diseases	1.92 (0.82-4.52)	0.1
Atrophy (open type)	3.06 (1.10-8.49)	0.03
Intestinal metaplasia	4.39 (1.58-12.2)	0.005
GX	5.64 (2.47-12.9)	<0.0001

GX: gastric xanthoma, OR: odds ratio

Table 5. Comparison of Clinical Features of the Two Groups (Atrophy-matched Control Analysis).

Characteristic	Group C (n=70)	Group NC (n=70)	p value
Age, median [IQR], years	70 [64-75]	68 [61.25-75.75]	0.5
Male sex, n (%)	65 (92.9)	42 (60.0)	<0.0001
DM, n (%)	19 (27.1)	12 (17.1)	0.2
Other malignant disease, n (%)	33 (47.1)	15 (21.4)	0.003
Intestinal metaplasia, n (%)	63 (90.0)	41 (58.6)	0.0001
GX, n (%)	45 (64.3)	11 (15.7)	<0.0001

IQR: interquartile range

Table 6. Conditional Logistic Regression Analysis of Predictive Markers for Gastric Cancer Detected after *Helicobacter Pylori* Eradication (Atrophy-matched Control Analysis).

Variable	OR	p value
Male sex	4.25 (1.06-17.1)	0.04
Other malignant diseases	3.90 (1.03-14.8)	0.04
Intestinal metaplasia	2.32 (0.60-8.96)	0.2
GX	14.30 (2.91-70.4)	0.001

GX: gastric xanthoma, OR: odds ratio

summarized in Table 5. Atrophy (open type) of both groups was 63 (90.0%) together. The age did not differ significantly between the two groups. The proportions of men, other malignant diseases, intestinal metaplasia and GX were significantly higher in Group C than in Group NC. Male sex, complications with other malignant diseases, the presence of intestinal metaplasia and GX were included in the conditional logistic regression analysis. Male sex, other malignant diseases and GX were confirmed as independent predictors for GC detected after *H. pylori* eradication (Table 6).

Discussion

We compared the characteristics of 70 patients with GC to those of 114 outpatients of our department without GC after *H. pylori* eradication to investigate predictive markers for early GC detected after *H. pylori* eradication. A multivariate logistic regression analysis identified male sex, atrophy (open type), the presence of intestinal metaplasia and GX as being independent predictive markers for early GC detected after *H. pylori* eradication. An atrophy-matched control analysis also identified GX as an independent predictor.

A recent prospective study reported that the incidence of GC after *H. pylori* eradication was 0.21% per year, and older age and severe atrophy were risk factors for GC after *H. pylori* eradication (19). Another recent retrospective cohort study reported that atrophy and intestinal metaplasia were predictors for GC after *H. pylori* eradication (20). In this study, atrophy and intestinal metaplasia, but not older age, were associated with early GC detected after *H. pylori* eradication.

The endoscopic findings related to the risk of GC have been previously reported (3, 7-10), with five specifically designated as predictive markers: atrophy, intestinal metaplasia, fold enlargement, nodularity and diffuse redness. A subsequent study reported scores for endoscopic findings related to the risk of GC (12). However, the effectiveness of these scores remained unclear. After performing a univariate analysis, we conducted a multivariate logistic regression analysis using atrophy and intestinal metaplasia as variables. Our findings indicated that atrophy (open type) and the presence of intestinal metaplasia were predictive markers for early GC detected after *H. pylori* eradication. However, further investigations are needed to evaluate the effectiveness of these scores.

GX, a localized non-neoplastic accumulation of foamy histiocytes in the lamina propria of the inflamed gastric mucosa, is occasionally detected during EGD (21). The presence of GX is a positive indicator of *H. pylori* infection and

persists after *H. pylori* eradication therapy. GX has received little clinical attention, perhaps because it is considered a benign entity (15). A retrospective cohort study reported that the presence of GX was significantly associated with the presence of GC (13, 14). Another cohort study reported that the presence of GX was a useful marker for predicting the development of GC by performing follow-up EGD (15). We also reported that the presence of GX was a predictive marker for metachronous and synchronous GC (16). However, those studies (13-16) did not investigate the presence of GX as a predictive marker for GC detected after *H. pylori* eradication. In the present study, a univariate analysis revealed that there was a significantly greater proportion of patients with GX in Group C than in Group NC. In addition, a multivariate logistic regression analysis indicated that the presence of GX was a predictive marker for early GC detected after *H. pylori* eradication. An atrophy-matched control analysis also identified GX as an independent predictor. To our knowledge, this is the first study to confirm the presence of GX as an independent predictive marker for early GC detected after *H. pylori* eradication.

Regarding why GC develops more frequently in patients with GX than in those without GX, the increased release of oxygen free radicals may be involved in the formation of GX (22). Conversely, the presence of GX may reflect the severity and long duration of chronic gastritis (14), a risk factor for the development of GC. In fact, the proportion of patients with atrophy (open type) and the atrophy score of patients were significantly higher in Group C than in Group NC. In fact, atrophy was significantly associated with GX in this study. However, further studies are required to clarify this link.

Our study has several limitations, including its retrospective single-center study design, the relatively small sample sizes, the inclusion of only patients with early GC who underwent ESD, and the lack of an evaluation of the interobserver variability in the assessment of endoscopic images.

In conclusion, we showed in the present study that male sex, atrophy (open type), the presence of intestinal metaplasia and GX were independent predictive markers for early GC detected after *H. pylori* eradication. An atrophy-matched control analysis also identified GX as an independent predictor. These findings, especially the predictive value of the presence of GX, may help improve the timely detection of early GC after *H. pylori* eradication. However, further investigations are needed to confirm the utility of these markers.

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

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