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World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJGO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

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Observational Study

Gastric xanthoma is a predictive marker for metachronous and synchronous gastric cancer

Narihiro Shibukawa, Shohei Ouchi, Shuji Wakamatsu, Yuhei Wakahara, Akira Kaneko

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Abstract**AIM**

To investigate predictive markers for metachronous and synchronous gastric cancer (GC), which can develop after endoscopic submucosal dissection (ESD).

METHODS

A total of 352 patients underwent ESD for early GC at NTT West Osaka Hospital between June 2006 and February 2016. Exclusion criteria were as follows: Remnant stomach, unknown *Helicobacter pylori* status, and endoscopic observation of the whole stomach outside our hospital. We analyzed data from 192 patients comprising 109 patients with solitary GC (Group A) and 83 with metachronous and synchronous GC (Group B). We retrospectively investigated the clinicopathological and endoscopic characteristics, and endoscopic risk score as predictive markers for GC.

RESULTS

The median age of Group B [72 years (interquartile range 63-78)] was significantly higher than that of Group A [66 years (interquartile range 61-74), respectively, $P = 0.0009$]. The prevalence of intestinal metaplasia in Group B tended to be higher than that in Group A (57.8% vs 45.0%, $P = 0.08$). The prevalence of gastric xanthoma (GX) in Group B was significantly higher than that in Group A (54.2% vs 32.1%, $P = 0.003$). The atrophy score in Group B was significantly higher than that in Group A ($P = 0.005$). Multivariate analysis revealed that higher age and the presence of GX were independently related to metachronous and synchronous GC [OR = 1.04

(1.01-1.08), $P = 0.02$; and OR = 2.11 (1.14-3.99), $P = 0.02$, respectively].

CONCLUSION

The presence of GX is a useful predictive marker for metachronous and synchronous GC.

Key words: Gastric cancer; Metachronous neoplasms; Synchronous neoplasms; Xanthoma; Biomarker

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Core tip: This was a retrospective observational study to identify predictive markers for metachronous and synchronous gastric cancer (GC). Multivariate analysis revealed that higher age and the presence of gastric xanthoma were independently related to the development of metachronous and synchronous GC. Additional large prospective studies are necessary to investigate this important issue further.

Shibukawa N, Ouchi S, Wakamatsu S, Wakahara Y, Kaneko A. Gastric xanthoma is a predictive marker for metachronous and synchronous gastric cancer. *World J Gastrointest Oncol* 2017; 9(8): 327-332 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v9/i8/327.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v9.i8.327>

INTRODUCTION

Endoscopic submucosal dissection (ESD) is currently accepted as an effective and minimally invasive treatment for early gastric cancer (GC)^[1-7]. However, the development of metachronous and synchronous GC remains a possibility after ESD^[8-14]. Predictive markers for the development of metachronous and synchronous GC have not been extensively studied. In addition, it is often difficult to clearly distinguish metachronous GC from synchronous GC because of missed detection of synchronous GC.

The cumulative incidence of metachronous GC after endoscopic resection for early GC ranges from 5.2% to 22.7%^[8-14]. The incidence of missed detection of synchronous GC was reported to be between 1.2% and 7.7%^[15,16]. In 2015, the Kyoto global consensus report on *Helicobacter pylori* (*H. pylori*) gastritis was published^[17]. At the same time, an endoscopic score for GC risk was also announced^[18]. Also, gastric xanthoma (GX) has been reported as the predictive marker of early GC^[19,20].

The usefulness of endoscopic score for GC risk as an accurate predictor of GC risk remains unclear. And the utility of GX as a predictive marker of metachronous and synchronous GC also remains unknown.

Therefore, we performed a retrospective study to investigate predictive markers of the development of metachronous and synchronous GC, including GX and

endoscopic score for GC risk.

MATERIALS AND METHODS

Patients

This study was a retrospective, single-center, observational study. Between June 2006 and February 2016, a total of 352 patients underwent ESD for early GC at NTT West Osaka Hospital. Exclusion criteria for this study were as follows: Remnant stomach, unknown *H. pylori* status, and endoscopic observation of the whole stomach outside our hospital. Finally, 192 patients including 109 with solitary GC (Group A) and 83 with metachronous and synchronous GC (Group B), were included in the study (Figure 1). Solitary GC was defined as no past history of GC and only one GC that developed during the study period. Metachronous and synchronous GC were defined as a new GC that developed in an area other than the site of primary GC and multiple GC that developed at the same endoscopic examination. The following factors were examined: Age, sex, complicated with diabetes mellitus, complicated with other malignant disease, *H. pylori* status, tumor location, tumor size, macroscopic type, histological type, tumor depth, endoscopic score for GC risk, and presence of severe atrophy, intestinal metaplasia, and GX. Presence of *H. pylori* infection was determined by serum antibody, rapid urease test, immunohistochemistry, ¹³C urea breath test, or stool antigen test. Endoscopic images were evaluated at the time of GC diagnosis or ESD. Endoscopic images were reviewed by one expert endoscopist. We classified the severity of gastric atrophy according to the criteria of Kimura and Takemoto^[21]. Severe atrophy was classified as O-2, 3, and P. O-P was the state that gastric atrophy progressed in the whole stomach. We diagnosed presence of GX as yellowish-white flat or slight elevated lesion by white light imaging. Endoscopic score for GC risk was calculated as follows: (1) atrophy: 0 if C-0 and 1, 1 if C-2 and 3, 2 if O-1, 2, 3, and P; (2) intestinal metaplasia: 0 if absent, 1 if present at gastric antrum, 2 if present at gastric antrum and body; (3) fold swelling: 0 if absent, 1 if present; (4) nodular gastritis: 0 if absent, 1 if present; and (5) diffuse redness: 0 if absent, 1 if mild, 2 if severe. For assessment of intestinal metaplasia, image-enhanced endoscopy with distinct white light imaging was necessary. In this study, we evaluated intestinal metaplasia as grayish-white flat elevated lesion by white light imaging, without image-enhanced endoscopy. This study was carried out with the approval of the NTT West Osaka Hospital Ethics Committee. Because of the anonymous nature of the data obtained after each patient had provided written informed consent for ESD, the requirement for informed consent was waived.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University,

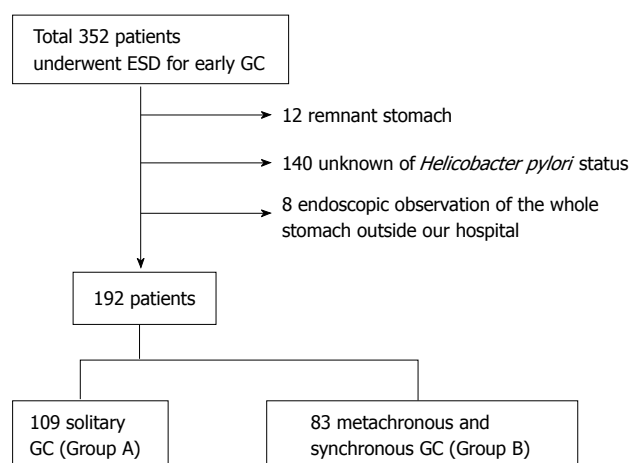


Figure 1 Flow diagram for the study. ESD: Endoscopic submucosal dissection; GC: Gastric cancer.

Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics^[22]. Fisher's exact test was performed to investigate the relationships between the two groups. Differences between the two groups were analyzed by Mann-Whitney *U* test when the data was not parametric. Multivariate logistic analysis was used to identify predictive markers of metachronous and synchronous GC. Age, sex, and baseline variables with $P < 0.2$ in univariate analysis were included in the multivariate logistic analysis. The threshold for significance was $P < 0.05$.

RESULTS

Clinicopathological characteristics of patients

The characteristics of the two patient groups are shown in Table 1.

The median ages in Group A and B were 66 [interquartile range (IQR) 61-74] and 72 (IQR 63-78) years, respectively ($P = 0.0009$). The proportion of male patients was high in both groups (84.4% vs 86.7%, $P = 0.7$). *H. pylori* status was positive for many patients in Group A and B (75.2% vs 68.7%, respectively, $P = 0.4$).

Regarding tumor location, lesion of the upper part of the stomach was least frequent. Median tumor size was 15 mm in both groups. The most frequent macroscopic type was 0-II a and the most frequent histological type was the differentiated type.

Endoscopic characteristics

Endoscopic characteristics are shown in Table 2. Although the difference was not significant, the prevalence of severe atrophy and intestinal metaplasia in Group B tended to be higher than that in Group A (89.2% vs 79.8%, $P = 0.1$ and 57.8% vs 45.0%, $P = 0.08$). The prevalence of GX in Group B was significantly higher than that in Group A (54.2% vs

Table 1 Clinicopathological characteristics of the two groups *n* (%)

	Group A (<i>n</i> = 109)	Group B (<i>n</i> = 83)	<i>P</i> value
Age, median [IQR], yr	66 [61-74]	72 [63-78]	0.0009
Male	92 (84.4)	72 (86.7)	0.7
Diabetes mellitus	24 (22.0)	12 (14.5)	0.2
Complicated other malignant disease	27 (24.8)	22 (26.5)	0.9
<i>Helicobacter pylori</i> status			0.4
Positive	82	57	
Post eradicated	23	26	
Negative	4	0	
Tumor location			0.9
Upper	10	11	
Middle	57	39	
Lower	42	33	
Tumor size, median [IQR], mm	15 [10-20]	15 [12-22]	0.3
Macroscopic type			0.5
0-I	9	3	
0-II a	67	52	
0-II b	26	25	
0-II c	7	3	
Differentiated type	109 (100)	81 (97.6)	0.2
Tumor depth			0.1
M	97	80	
SM	12	3	

IQR: Interquartile range; M: Mucosal; SM: Submucosal.

32.1%, $P = 0.003$). The number and size of GX were not significantly different between the two groups.

Endoscopic score for GC risk

The endoscopic score for GC risk is reported in Table 3. The atrophy score in Group B was significantly higher than that in Group A ($P = 0.005$). The scores for intestinal metaplasia, fold swelling, and diffuse redness, and the total score were not significantly different between the two groups. Nodular gastritis was absent in all patients in this study.

Multivariate logistic analysis

Age, male sex, severe atrophy, presence of intestinal metaplasia, and presence of GX were subjected to multivariate logistic analysis. As shown in Table 4, higher age and the presence of GX were independently related to metachronous and synchronous GC.

DISCUSSION

In the present study, we compared the characteristics of 109 patients with solitary GC to those of 83 patients with metachronous and synchronous GC in order to identify predictive markers for metachronous and synchronous GC. Multivariate logistic analysis revealed that high age and the presence of GX were independently related to metachronous and synchronous GC.

The results of recent studies indicated that male sex, multiple initial GC, severe atrophy, and multiple GC before successful *H. pylori* eradication were independent risk factors for metachronous GC^[13,14]. After performing

Table 2 Endoscopic characteristics of the two groups *n* (%)

	Group A (<i>n</i> = 109)	Group B (<i>n</i> = 83)	<i>P</i> value
Severe atrophy	87 (79.8)	74 (89.2)	0.1
Intestinal metaplasia	49 (45.0)	48 (57.8)	0.08
Gastric xanthoma	35 (32.1)	45 (54.2)	0.003

Table 3 Endoscopic score of risk for gastric cancer of the two groups

	Group A (<i>n</i> = 109)	Group B (<i>n</i> = 83)	<i>P</i> value
Atrophy			0.005
0	4	0	
1	6	0	
2	99	83	
Intestinal metaplasia			0.1
0	60	35	
1	33	34	
2	16	14	
Fold swelling			0.6
0	99	73	
1	10	10	
Nodular gastritis			1.0
0	109	83	
1	0	0	
Diffuse redness			0.5
0	4	0	
1	23	25	
2	82	58	
Total score, median [IQR]	4 [4-5]	4 [4-5]	0.1

IQR: Interquartile range.

univariate analysis, we carried out multivariate logistic analysis using male sex and severe atrophy as variates, but our results revealed that these two markers were not predictive of metachronous and synchronous GC. This finding may reflect the fact that most patients in this study were male and showed severe atrophy in both groups.

Endoscopic findings related to the development of GC have been previously reported^[23-27]. Of these, five endoscopic findings were confirmed; atrophy, intestinal metaplasia, fold swelling, nodular gastritis, and diffuse redness. A subsequent study reported the endoscopic score for GC risk^[18]; however, the usefulness of this score remains unclear. After performing univariate analysis, we carried out multivariate logistic analysis using severe atrophy and intestinal metaplasia as variates. However, our results indicated that these two markers were not predictive of metachronous and synchronous GC. Further investigations are necessary to evaluate the usefulness of the endoscopic score for GC risk.

GX, a localized non-neoplastic accumulation of foamy histiocytes in the lamina propria of the inflamed gastric mucosa, is occasionally found during EGD^[28]. GX is a positive indicator of *H. pylori* and persists after

Table 4 Multivariate analysis of predictive marker of metachronous and synchronous gastric cancer

	Odds ratio	<i>P</i> value
Age	1.04 (1.01-1.08)	0.02
Male	1.38 (0.57-3.34)	0.47
Severe atrophy	1.68 (0.70-4.05)	0.25
Intestinal metaplasia	1.35 (0.71-2.54)	0.36
Gastric xanthoma	2.11 (1.14-3.99)	0.02

H. pylori eradication therapy. GX has received little attention clinically, perhaps because it is considered a benign entity^[20]. A retrospective cohort study reported that the presence of GX was significantly associated with the presence of GC^[19]. Another cohort study performed at the same hospital reported that GX was a useful marker for predicting the development of GC by performing endoscopic follow-up examinations^[20]. However, both these studies did not investigate GX as a predictive marker for metachronous and synchronous GC. In our study, univariate analysis revealed that GX was significantly more prevalent in Group B than in Group A. In addition, results of multivariate logistic analysis indicated that GX was a predictive marker for metachronous and synchronous GC. To our knowledge, this is first report of the presence of GX as a useful predictive marker for metachronous and synchronous GC.

Why does GC develop more frequently in patients with GX? Increased release of oxygen free radicals may be involved in the formation of GX^[29]. On the other hand, the presence of GX may reflect the severity and long duration of chronic gastritis^[20], which is a risk factor for GC development. Because of the same reason, GX may be more frequent in Group B than Group A. However, further studies are required to elucidate this link.

Our study has some limitations. First, it was a retrospective single-center study. Second, the sample size was small. Finally, we did not analyze inter-observer variability in the assessment of endoscopic images.

In summary, our results revealed that higher age and the presence of GX were independently related to metachronous and synchronous GC. These findings, especially the predictive value of the presence of GX, could improve the timely detection and treatment of metachronous and synchronous GC. Further investigations are necessary to confirm the predictive value of these markers.

COMMENTS

Background

Predictive markers for the development of metachronous and synchronous gastric cancer (GC) have not been extensively studied. In addition, it is often difficult to clearly distinguish metachronous GC from synchronous GC because of missed detection of synchronous GC. And the usefulness of endoscopic score for GC risk and gastric xanthoma (GX) as the predictive markers of metachronous and synchronous GC remains unknown.

Research frontiers

This study investigated the predictive markers for metachronous and synchronous GC.

Innovations and breakthroughs

Higher age and the presence of GX were independently related to the development of metachronous and synchronous GC.

Applications

GX is a useful predictive marker for metachronous and synchronous GC.

Terminology

Solitary GC is defined as no past history of GC and only one GC that developed during the study period. Metachronous and synchronous GC are defined as a new GC that developed in an area other than the site of primary GC and multiple GC that developed at the same endoscopic examination.

Peer-review

This is a retrospective study to investigate predictive markers for metachronous and synchronous GC developing after endoscopic submucosal dissection. This is good idea for clinics.

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