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Clinical outcomes of endoscopic surveillance for gastric ulcers in populations with a high prevalence of gastric cancer

STOMACH

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Original Article

ABSTRACT

Background/Aims: Although surveillance endoscopy is recommended after the treatment of a benign gastric ulcer in Korea, improved survival, secondary to an endoscopic follow-up strategy, is controversial. Thus, the aim of this study was to understand the results of gastric ulcer surveillance endoscopy and to individualize surveillance endoscopy by analyzing known risk factors for gastric cancer.

Materials and Methods: In total, 599 (M:F=424:175, median age=55.4 years) patients who were diagnosed with a gastric ulcer and who underwent follow-up endoscopy between January 2003 and August 2014 were retrospectively enrolled in this study. The final results and risk factors of follow-up endoscopy were analyzed.

Results: Multivariate analysis of the data between the benign and malignant ulcer groups (benign: malignant=575:24) showed that an elevated border and irregular margins, among other risk factors, were significant indicators of malignancy ($p<0.05$). Of the 599 patients, 15 (2.5%) were histologically malignant based on the first biopsy results. Nine (1.5%) patients had malignant ulcers on surveillance endoscopy, and all nine were found to have atypia or dysplasia on the first biopsy. Eight of the nine patients had malignant endoscopic features.

Conclusion: Surveillance endoscopy for gastric ulcers may be unnecessary, except in cases of malignant and pre-malignant endoscopic features on the initial endoscopy.

Keywords: Stomach ulcer, stomach neoplasm, follow-up studies, endoscopy, risk factors

INTRODUCTION

Peptic ulcers are common in patients presenting to the gastroenterology department, with an annual incidence of 0.10–0.19% in physician-diagnosed data and 0.03–0.17% in hospital-based data (1). The prevalence of peptic ulcers is approximately 10% in Korea (2) and more than five per 1,000 adults in the United States (3). Although the vast majority of peptic ulcers are benign, gastric ulcers pose a malignancy risk in patients who use non-steroidal anti-inflammatory drugs (NSAIDs) or are infected with *Helicobacter pylori (H. pylori)*. In addition, approximately 5% of endoscopic benign-appearing gastric ulcers are malignant (4,5). Although the current British guidelines recommend that all gastric ulcers should be followed with repeated endoscopy and biopsy until they heal (6,7), the American Society for Gastrointestinal Endoscopy does not recommend routine endoscopic surveillance for patients with gastric ulcers (8). Surveillance endoscopy is recommended in Korea at 4–8 weeks after the treatment of a benign gastric ulcer (9). The rate of endoscopic surveillance in the United States is higher (65%) than expected (10), and the overuse of surveillance esophagogastroduodenoscopy (EGD) in patients with gastric ulcers may increase procedural-related complications and costs. The quality of endoscopy using magnifying narrow-band imaging to diagnose early gastric cancer has improved (11), and the incidence of gastric cancer has decreased in Korea (12) and other parts of the world (13). A few studies have recommended individualized surveillance endoscopy (6,14). However, no study has examined the results of surveillance EGD in Korea, and improved survival, secondary to an endoscopic follow-up strategy, remains controversial.

Thus, the aim of the present study was to understand the results of gastric ulcer surveillance endoscopy and

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to individualize surveillance endoscopy by analyzing known risk factors for gastric cancer.

MATERIALS AND METHODS

The study protocols were reviewed and approved by the institutional review board of the hospital according to the ethical guidelines of the Declaration of Helsinki. Written informed consent was not required because of the retrospective nature of this investigation.

Patients

We performed a retrospective case-control study on the results of gastric ulcer surveillance endoscopy to identify risk factors for gastric cancer using data from the electronic medical records at a single center. Patients diagnosed with gastric ulcer who underwent follow-up endoscopy at a teaching hospital in Korea between January 2003 and August 2014 were enrolled retrospectively in this study. The cases were selected by searching the electronic medical records for the term "gastric ulcer" on endoscopic diagnostic reports. Inclusion criteria were as follows: (i) patient age>18 years and (ii) initial and follow-up biopsy by EGD. Exclusion criteria included the following: (i) too early (<1 week) or too late (>3 months) follow-up endoscopy; (ii) iatrogenic gastric ulcer; (iii) ulcers without biopsy; and (iv) patient <18 years old.

Study protocol

Patients were classified into benign and malignant ulcer groups. The variables used to determine gastric cancer risk were: (i) age; (ii) sex; (iii) drug use (NSAIDS, aspirin); (iv) *H. pylori* infection; (v) associated bleeding; (vi) ulcer number, size, and location; and (vii) ulcer margin, border, and base. The Paris classification and the Japanese Classification of Gastric Cancer were used to describe all lesions (15,16). The endoscopically malignant characteristics of the ulcers included irregular margin, elevated border, and dirty base. These are common criteria for discriminating malignant and benign ulcers and are commonly used in endoscopic and related studies (6,17). All endoscopic pictures of the subjects in this study were re-evaluated for the endoscopic characteristics (base, edges, and folds) by two experienced endoscopists to accurately determine any malignant-like ulcers.

Both endoscopists were blinded to the biopsy results. Endoscopically malignant ulcers were defined by strict criteria. Ulcers with at least one of the three endoscopic characteristics was defined as malignant. Figure 1 shows examples.

EGD and data definitions

Index EGD was defined as the initial EGD performed. Surveillance EGD was defined as any EGD performed within 3 months

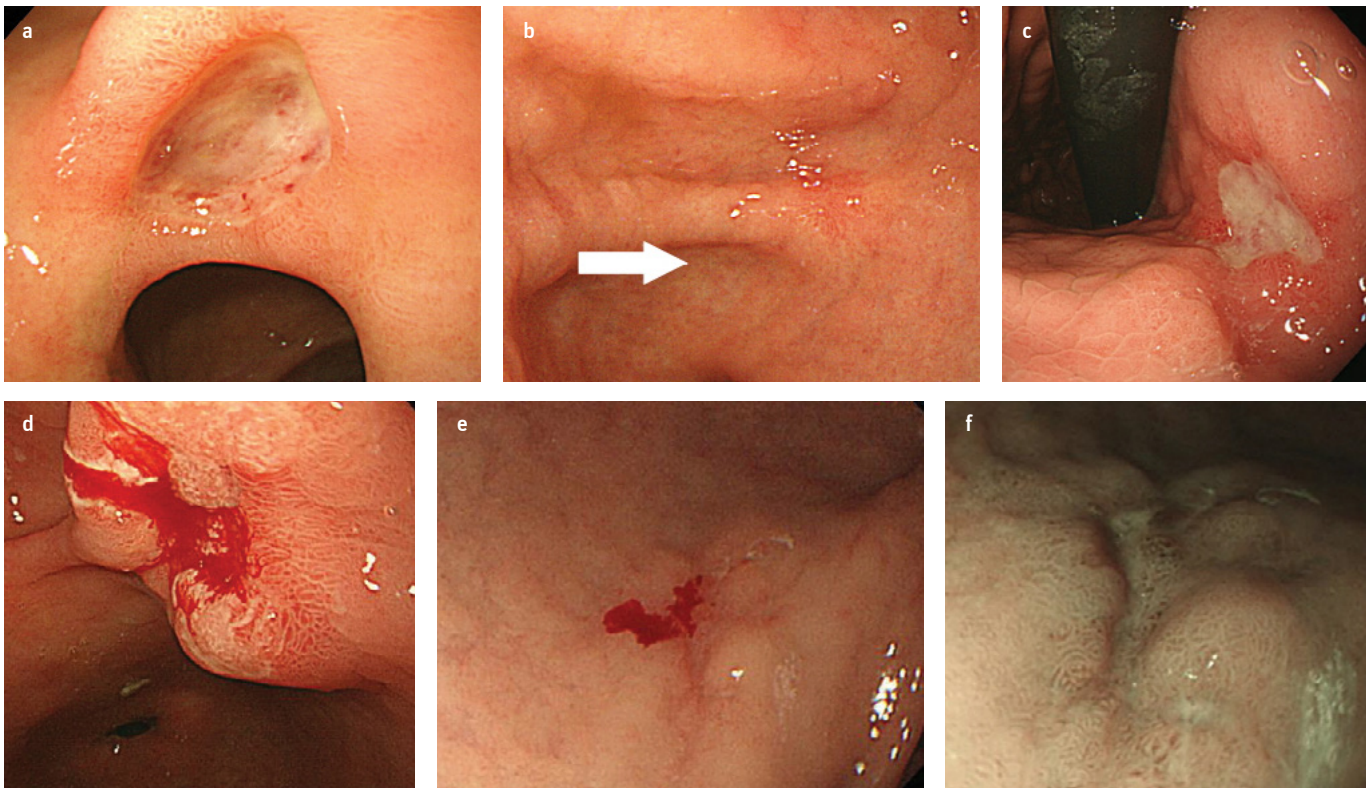

Figure 1. a-f. Benign-looking gastric ulcer (<1 cm) at the antrum (a). The ulcer has a clean base and has no elevated border or irregular margin. A scar (arrow) is visible at 2-month follow-up endoscopy (b); the biopsy confirmed no malignancy. Gastric ulcer (3 cm) located in the body (c). The ulcer has a clean base and no elevated border but has an irregular margin. This lesion was classified as a malignant-looking ulcer, and histology showed malignancy. Malignant-looking gastric ulcer with a touch of bleeding located in the antrum (d). The ulcer has elevated borders and an irregular margin but has a clean base. Slightly depressed lesion with a touch of bleeding on antrum in an image obtained from white-light imaging (e). Image obtained from narrow band imaging shows clearer visualization of a margin and base (f). Final classification of this lesion was as a malignant-looking gastric ulcer.

of the index examination. All endoscopic procedures were done using a white-light endoscope with narrow band imaging (GIF-H260, Olympus; Tokyo, Japan). All lesions were measured with endoscopic forceps (FB-24K-1, Olympus; Tokyo, Japan).

The presence of an *H. pylori* infection was defined by either a positive rapid urease test or demonstration of *H. pylori* on a Giemsa-stained histological specimen.

Statistical analyses

Statistical analysis was performed using the crosstab test and a univariate analysis, except for age, which was analyzed with an independent sample *t*-test. Logistic regression was used for the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A p value <0.05 was considered significant. SPSS for Windows ver. 11 software (SPSS Inc.; Chicago, IL, USA) was used for all analyses.

RESULTS

Patient characteristics

In total, 1,012 patients were enrolled. Of these, 223 were excluded because of a limited follow-up duration. Of the 223 patients, 123 were excluded because they underwent endoscopy within 1 week. Physicians at our institution usually perform a second-look endoscopy on the next day when re-bleeding is suspected. Another 100 patients were excluded because they underwent follow-up endoscopy after 3 months. Fifty-eight iatrogenic ulcers were excluded because most were post-procedural ulcers that developed after endoscopic submucosal dissection for early gastric cancer. In addition, 132 patients who had not undergone a biopsy were excluded. Thus, 599 patients (M:F=424:175, median age=55.4 years) were included in the study (Figure 2). Of the 599 patients, 575 were histologically proven to be benign on both index and follow-up endoscopy. The ulcers in 24 patients were histologically proven to be malignant on index or follow-up endoscopy. Endoscopically malignant gastric ulcers are described as advanced or early gastric cancer at our institution, thereby making the incidence of malignant ulcers low in this study.

Risk factors for gastric cancer among the gastric ulcers

Age, sex, NSAID or aspirin use, and the presence of *H. pylori* were not significantly associated with malignancy (Table 1). A univari-

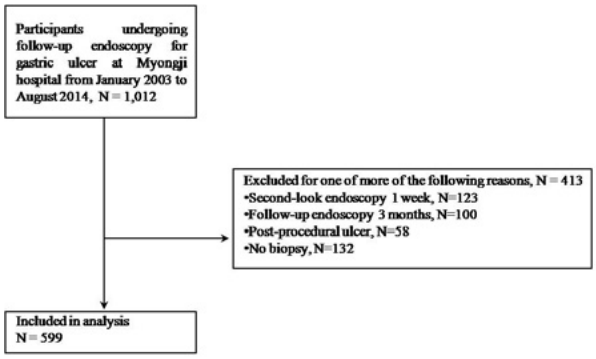

Figure 2. Selection of the study participants with gastric ulcers

Table 1. Univariate analysis of demographic features in patients with a gastric ulcer

Variable	Total (N=599)	Benign (N=575)	Malignancy (N=24)	OR (95% CI)	p
Age	55.4±13.5	55.3±13.5	58.8±13.8		0.215
Sex			1.595 (0.58–4.34)	0.357	
Male	424	405	19		
Female	175	170	5		
NSAIDS except aspirin				0.563 (0.16–1.97)	0.364
Yes	48	45	3		
No	525	506	19		
Missing	26	24	2		
Aspirin				0.816 (0.23–2.83)	0.749
Yes	66	63	3		
No	508	489	19		
Missing	25	23	2		
H. pylori infection				0.855 (0.36–2.01)	0.720
Yes	332	320	12		
No	238	228	10		
Missing	29	27	2		

Values are presented as mean±standard deviation or numbers.
OR: odd ratio; CI: confidence interval; NSAID: non-steroidal anti-inflammatory drug

Table 2. Univariate analysis of the endoscopic features in patients with gastric ulcers

Variable	Total (N=599)	Benign (N=575)	Malignancy (N=24)	OR (95% CI)	p
Number of ulcers				2.403 (0.98–5.88)	0.060
Single	306	289	17		
Multiple	293	286	7		
Size of ulcers				1.934 (0.85–4.38)	0.109
<1 cm	391	379	12		
≥1 cm	208	196	12		
Location of ulcers				1.085 (0.47–2.46)	0.846
Antrum	336	323	13		
Not-antrum	263	252	11		
Dirty base				2.53 (0.82–7.76)	0.091
Yes	46	42	4		
No	553	533	20		
Elevated border				4.457 (1.82–10.86)	<0.001*
Yes	66	58	8		
No	533	517	16		
Irregular margin				15.446 (6.46–36.91)	<0.001*
Yes	71	56	15		
No	528	519	9		
Bleeding				1.102 (0.32–3.79)	0.878
Yes	69	66	3		
No	530	509	21		

Values are presented as number.
OR: odds ratio; CI: confidence interval
*Statistically significant.

ate analysis of the benign and malignant ulcer group data, considering the endoscopic features, showed that an elevated border (2.9% vs. 12.1%, p<0.001) and irregular margin (1.7% vs. 21.1%, p<0.001) were significant indicators of malignancy. Single ulcer (p=0.06) and a dirty ulcer base (p=0.09) tended to be associated with malignancy (Table 2). The size and location of the ulcer and the presence of bleeding were not significantly associated with malignancy. The multivariate analysis revealed that an elevated border (adjusted OR=5.339, p=0.003) and irregular margin (adjusted OR=23.481, p<0.001) were significantly associated with malignancy (Table 3). In addition, the number of ulcers (p=0.08) and a dirty base (p=0.07) tended to be associated with malignancy.

Table 3. Multivariate analysis of demographic and endoscopic features in patients with gastric ulcers

Variable	Adjusted OR (95% CI)	p
Number of ulcers	2.565 (0.88–7.45)	0.084
Dirty base	3.734 (0.89–15.65)	0.072
Elevated border	5.339 (1.75–16.24)	0.003*
Irregular margin	23.481 (7.95–69.33)	<0.001*

OR: odds ratio; CI: confidence interval
*Statistically significant.

Characters of patients with malignancy on surveillance endoscopy

Figure 3 shows a flow-chart for this study. A total of 158 gastric ulcers had endoscopic features suggestive of malignancy, and 15 (2.5%) were malignant histologically on the first biopsy (ⓑ+ⓓ). Only nine (1.5%) patients had malignant ulcers on surveillance endoscopy (ⓕ+ⓗ). Only two of 441 patients with endoscopically benign features (ⓑ) had malignant ulcers histologically on the first biopsy; one patient with atypia on the first biopsy (ⓕ) had a malignant ulcer on the surveillance biopsy (Figure 3). All nine patients whose surveillance endoscopy indicated a malignancy (ⓕ+ⓗ) were judged as atypia or dysplasia on the first biopsy. Eight patients (ⓗ) had endoscopically malignant features (Table 4).

DISCUSSION

In some countries, including Korea, surveillance endoscopy is recommended after treatment of a benign gastric ulcer (18).

Table 4. Characteristics of patients with a malignancy on surveillance endoscopy

Patient	Sex/age	Number of ulcers	Endoscopic malignant feature	Initial pathology	Surveillance pathology
1	M/84	Single	-	Atypia	Adenocarcinoma, well differentiated
2	M/62	Multiple	Elevated border, irregular margin	Atypia	Adenocarcinoma, well differentiated
3	F/52	Single	Irregular margin	Atypia	Adenocarcinoma, poorly differentiated
4	M/68	Multiple	Irregular margin	Atypia	Adenocarcinoma, well to poorly differentiated
5	M/47	Single	Irregular margin	Atypia	Adenocarcinoma, well differentiated
6	M/45	Single	Dirty base, elevated border	Atypia	Adenocarcinoma, well differentiated
7	F/67	Multiple	Irregular margin	Atypia	Adenocarcinoma, poorly differentiated
8	M/51	Multiple	Irregular margin	LGD	Adenocarcinoma, moderate to poorly differentiated
9	F/69	Single	Irregular margin	LGD	Adenocarcinoma, well differentiated

M: male; F: female; LGD: low-grade dysplasia

Yet improvements in survival, secondary to an endoscopic follow-up strategy, are controversial. To the best of our knowledge, this is the first study in South Korea about surveillance endoscopy of gastric ulcers. Among the 439 patients with endoscopically benign features in this study, only one had a malignant diagnosis based on histology after the surveillance endoscopic biopsy. The patient (patient number 1 in Table 4) had atypia on the first biopsy. Therefore, 438 cases of patients without pre-malignant pathology and endoscopically malignant appearance could have avoided surveillance endoscopy, which saves costs and avoids the complications and inconvenience of surveillance endoscopy.

A few previous studies showed that overall endoscopic and bioptic accuracy rates are very high at 97.4 to 98.8% (19,20). Thus, initial gastroscopy has higher diagnostic accuracy than that of the second-look gastroscopy. These findings are inconsistent with results that the follow-up of patients with repeated multiple biopsies may increase the sensitivity for a malignancy diagnosis in patients with gastric ulcers (21,22). However, many studies showed a low yield of follow-up endoscopy for gastric ulcers when the initial endoscopy included an adequate inspection and histology (17,23-26). Moreover, the strategy of endoscopic surveillance has not been shown to improve survival (27) and is unlikely to be cost-effective unless prevalence of undetected malignancy is >6% (14).

In the current study, the endoscopic impression of a benign ulcer was incorrect in one case (0.2%), which is extremely low, compared with the reported rates of incorrect endoscopic diagnosis of 0.7–13.3% (24,28,29) because this study was done with magnified endoscopy with narrow band imaging, which more effectively diagnoses early gastric cancer compared with that of white-light imaging (11,30).

It is very hard to discriminate between malignant and benign ulcers in a clinical setting. Thus, many physicians perform surveillance endoscopy routinely in patients with a gastric ulcer.

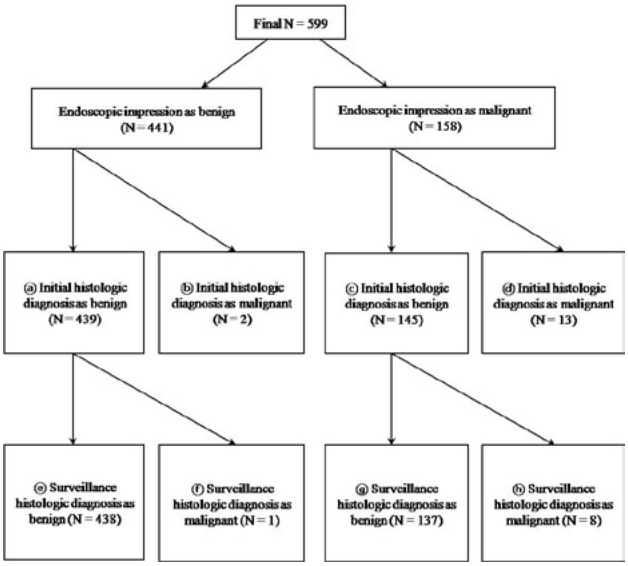

Figure 3. Flow chart of the patients with a gastric ulcer compared with endoscopic impression and histological diagnosis

Regardless of the guidelines, surveillance rates of Canadian and American endoscopists range from 16.0% to >60% (31,32). Although the annual age-standardized gastric cancer incidence rates per 100,000 are 65.9 (33) in Korean men vs. 7.8 (34) in non-Hispanic Caucasian men, only one cancer was found among the endoscopically benign ulcers in the current study, which had atypia on the first biopsy. Therefore, there might be no need for routine surveillance endoscopy in high risk areas.

Although our three endoscopic characteristics were subjective, the multivariate analysis revealed that an elevated border and an irregular margin were significant indicators of malignancy. In addition, a single ulcer and a dirty ulcer base tended to be associated with malignancy. Interestingly, ulcer size, location in the stomach, and other demographic characteristics were not associated with a high risk for malignancy. These findings are not in accord with another study reporting that the size of

an ulcer and its location in the stomach may be a marker for malignancy (35). Gastric ulcers >5 cm in diameter in the cardia region are particularly associated with a very high probability of malignancy. Endoscopic surveillance should be considered if other demographic risk factors are present, such as old age, family history of gastric cancer, and *H. pylori* infections (8,36,37). In the current study, the proportion of malignant ulcers was so small (benign:malignant=575:24) that it was difficult to define the risk factors for malignancy. Regardless of the demographic features, the three endoscopic features can exclude malignancy. Our results were well correlated with those of previous studies (17,38).

Our study had several limitations. First, the interpretation of gross endoscopic findings was subjective. The discrimination between benign and malignant ulcer depends on the endoscopist's experience or skill. The chance of falsely labeling an ulcer as benign was minimized by re-evaluating the endoscopic characteristics with two experienced gastroenterologists. Second, this study was a retrospective study; however, the cases were selected using strict exclusion criteria and a relatively large number of patients. Although we attempted to control for confounders, the potential for unmeasured confounding and bias remains. Third, the study was performed using data from a single center, so the number of gastric cancer cases was insufficient to calculate the risk factor. Thus, it may limit the generalization the findings to the general population. However, a strict gastric ulcer biopsy protocol was used because all endoscopies were conducted in the same hospital.

In conclusion, surveillance endoscopy for gastric ulcers may not be necessary except in cases of malignant features, including the base, margins, and borders, or pre-malignancy findings on the initial endoscopy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the institutional review board of Myongjin Hospital according to the ethical guidelines of the Declaration of Helsinki (MJH15-067).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.L.; Design - H.L.; Supervision - H.L.; Materials - Y.L.; Data Collection and/or Processing - Y.L.; Analysis and/or Interpretation - J.C.; Literature Review - J.H.; Writer - J.H., Y.L.; Critical Review - H.L.

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