Development of Metachronous Tumors after Endoscopic Resection for Gastric Neoplasm according to the Baseline Tumor Grade at a Health Checkup Center

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Background/Aims: Endoscopic resection (ER) procedure has been performed widely to treat gastric neoplasms. Here, we compared the long-term prognosis based on the clinical features of three types of recurred gastric neoplasms after ER, including low-grade dysplasia (LGD), high-grade dysplasia (HGD), and early gastric carcinoma (EGC).

Methods: Between 2003 and 2014, subjects who were diagnosed with gastric neoplasm during screening endoscopy were included. The baseline clinicopathologic and tumor recurrence were analyzed.

Results: Of the 316 patients enrolled, 170 patients (53.8%) were categorized into the LGD group, 34 patients (10.8%) into the HGD group, and 112 patients (35.4%) into the EGC group. The median follow-up duration was 4.2 years. Among the total, 14 patients experienced a development of metachronous gastric cancer; 4 patients (2.3%) in the LGD group, 3 patients (8.3%) in the HGD group, and 7 patients (6.1%) in the EGC group. Metachronous gastric neoplasm had developed in 17 LGD patients (10.0%), 5 HGD patients (14.7%), and 14 EGC patients (12.5%). There was no significant difference in the incidence of metachronous gastric cancer and neoplasm among the three groups (p=0.15 and p=0.72, respectively).

Conclusions: We identified that the incidence rates of gastric neoplasm and cancer after endoscopic treatment were not significantly different between the LGD, HGD, and EGC groups. (Korean J Gastroenterol 2017;70:223-231)

Key Words: Gastric neoplasm; Recurrence; Adenoma

INTRODUCTION

Stomach cancer is a common malignancy. Detection at an early stage reduces morbidity and improves survival. If there is no metastasis in the lymph nodes, the clinical outcome of early stage gastric cancer is very good, with a 5-year survival rate of 99%. Gastric dysplasia is considered as a premalignant lesion, suggesting an increased risk of gastric cancer according to the grade of the dysplasia.

Endoscopic resection (ER) has been widely performed to treat certain cases of gastric neoplasm. However, metachronous neoplasm can develop at another site in the stomach because the remnant mucosa may still be affected by precancerous lesions, such as, intestinal metaplasia or gastric...
atrophy, thus resulting in increased risk for recurrence. In fact, the incidence rate of metachronous or synchronous neoplasm after ER has been reported to be 3.0-20.9%. Previous studies have identified multiple predictors for metachronous neoplasm of the stomach, including *Helicobacter pylori* (*H. pylori*) infection, intestinal metaplasia or gastric atrophy, histologic findings, and grade of dysplasia. Therefore, scheduled endoscopic surveillance is important, especially for high risk patients who have undergone previous ER.

Clear guidelines regarding clinical management of gastric neoplasm after ER are lacking. Moreover, the recommended interval and period of follow-up exams vary widely. Thus, the purpose of this study was to investigate the long-term prognosis based on clinical features of three types of recurred gastric neoplasm after ER, including low grade dysplasia (LGD), high grade dysplasia (HGD), and early gastric cancer (EGC). The results of this study may guide individualized surveillance strategies based on the primary disease.

**SUBJECTS AND METHODS**

1. Patients

Between October 2003 and December 2014, subjects who were diagnosed with gastric neoplasm (LGD, HGD, and EGC) during a screening endoscopy at Seoul National University Hospital Healthcare System Gangnam Center were enrolled. The microscopic criteria of gastric neoplasm were defined in accordance with the Vienna classification; LGD in category 3, HGD in category 4, and invasive carcinoma in category 5.

Among the 406 cases of ER, 82 cases with less than 12 month of follow-up, 5 cases with additional operation immediately after ER, and 3 cases without ER due to old age were all excluded. This study was approved by the Institutional Review Board of Seoul National University; requirement for written consent was waived.

2. Endoscopy procedure and follow-up

In almost all cases, ER was performed with the endoscopic submucosal dissection (ESD) technique. Indications for ER were as follows: low- or high-grade dysplasia lesion regardless of tumor size and shape; if the lesion was EGC, histologically-confirmed adenocarcinoma with well or moderate-differentiation, with the depth of invasion confined to mucosa, a lesion less than 2 cm without evidence of distant or lymph node metastasis. Patients with LGD received several treatment modalities, including ESD, endoscopic ablation with argon plasma coagulation, endoscopic mucosal resection, or simple excisional biopsy, and regular surveillance endoscopy with re-biopsy when the size was less than 5 mm, based on the size of the lesion, endoscopist’s recommendation, as well as patient preference. After ER for gastric neoplasm, a follow-up endoscopy to detect any mucosal abnormalities was scheduled at 3, 6, and 12 months after ER, and annually thereafter. We defined local recurrence as a lesion found on the ER scar during a surveillance endoscopy. Metachronous lesion was defined as a lesion that had newly developed more than 1 year after the treatment of the primary lesion.

3. Clinicopathological evaluations

*H. pylori* infection was considered positive based on either positive findings on histological examination or a rapid urease test. Mucosal atrophy or intestinal metaplasia was considered to be present based on pathological examination. Endoscopic severity of gastric atrophy was assessed based on the location of the atrophic border via endoscopy, by distinctive differences in the visible capillary network, height of the gastric mucosa, and color, as reported by Kimura and Takemoto and Liu et al. The extent of EAG was categorized into six grades (C1 to O3) in accordance with the Kimura-Takemoto classification. We grouped the six categories into two types: antral dominant and corpus dominant types.

4. Statistics

Chi square test or Student’s t-test was performed to compare the baseline characteristics in accordance with the pathological type. Kaplan-Meier method with a log-rank test was performed to identify factors affecting tumor recurrence. Cox proportional hazard model was used to investigate the independent factors associated with increased risk of metachronous gastric neoplasm. All statistical analyses were performed using SPSS statistics for windows version 22.0 (SPSS Inc., Chicago, IL, USA). p-values of less than 0.05 were considered statistically significant.
RESULTS

1. Baseline characteristics of study population

During the study period, a total of 406 patients underwent ER for primary treatment of gastric neoplasm. Of these, 5 patients underwent additional gastrectomy due to incomplete ER. Moreover, we excluded 82 patients with less than 12 months of follow-up and 3 patients who refused endoscopic follow-up due to old age. The remaining 316 patients were enrolled for final analysis. Overall, the study included 249 males (79.1%) and 67 females (20.9%), with a mean age of 58.6±8.8 years (median 58 years, range 36-88 years). In total, 170 patients (53.8%) were categorized into the LGD group, 34 patients (10.8%) into the HGD group, and 112 patients (35.4%) into the EGC group (Fig. 1).

The baseline characteristics of the three groups are shown in Table 1. In the LGD group, the proportion of males was lower (72.9% vs. 88.2% and 84.8%; p=0.019) and the tumor size was smaller (8.3±4.5 mm vs. 11.6±6.9 mm and 14.2±9.0 mm; p<0.001). There were no significant differences among the three groups with respect to age, location of the primary tumor, lesion multiplicity, H. pylori infection, atrophy and intestinal metaplasia, follow-up duration, as well as the number of follow-up endoscopies. In total, 49 patients (28.8%) in the LGD group and one patient (2.9%) in the HGD group were treated using simple biopsy.

2. Development of metachronous neoplasm

The overall mean follow-up period was 4.5±2.4 years and ranged from 1.0 to 11.1 years (median 4.2 years). The longest interval between the initial ER and metachronous tumor recurrence was 6.3 years (range 1.1-6.3, median 3.2 years). During the follow-up period, a total of 14 metachronous gastric cancers were newly developed: 4 patients (2.3%) in the LGD group, 3 patients (8.3%) in the HGD group, and 7 patients (6.1%) in EGC group. The incidence rate of gastric cancer after endoscopy treatment was 15.2 cases per 1,000 person-years in the LGD group, 18.5 cases per 1,000 person-years in the HGD group, and 20.9 cases per 1,000 person-years in the EGC group. Metachronous gastric neoplasm developed in 17 LGD patients (10.0%), 5 HGD patients (14.7%), and 14 EGC patients (12.5%). The incidence of metachronous neoplasm was 28.6, 45.7, and 39.7 cases per 1,000 person-years in the LGD, HGD, and EGC groups, respectively.

The cumulative incidence of metachronous gastric cancer and neoplasm had no significant difference among the three groups via Kaplan-Meier analysis (p=0.15 and p=0.72, respectively, Fig. 2). When we combined the HGD and EGC groups, the cumulative incidence of metachronous gastric
Table 1. Clinical Characteristics according to the Pathologic Type of Initial Gastric Neoplasm

| Variables                                | LGD (n=170)       | HGD (n=34)       | Carcinoma (n=112) | p-value |
|-------------------------------------------|-------------------|------------------|-------------------|---------|
| Male gender                              | 124 (72.9)        | 30 (88.2)        | 95 (84.8)         | 0.019   |
| Age (years)                              | 59.1±8.7          | 57.7±10.0        | 59.5±9.1          | 0.557   |
| Tumor size (mm)                          | 8.3±4.5           | 11.6±6.9         | 14.2±9.0          | <0.001  |
| Location of primary lesion               |                   |                  |                   | 0.293   |
| Upper third                              | 4 (2.4)           | 2 (5.9)          | 6 (5.4)           |         |
| Middle third                             | 44 (26.0)         | 7 (20.6)         | 19 (17.0)         |         |
| Lower third                              | 121 (71.6)        | 25 (73.5)        | 87 (77.7)         |         |
| Multiple lesion                          | 7 (4.1)           | 3 (8.8)          | 10 (8.9)          | 0.227   |
| H. pylori infection                      | 79 (46.5)         | 17 (50.0)        | 66 (58.9)         | 0.126   |
| Atrophy                                  | 129 (75.9)        | 28 (82.4)        | 93 (83.0)         | 0.373   |
| Intestinal metaplasia                    | 93 (54.7)         | 22 (64.7)        | 63 (56.3)         | 0.631   |
| Endoscopic grade of atrophy              |                   |                  |                   |         |
| Antral dominant                          | 35 (20.6)         | 9 (23.5)         | 24 (21.4)         | 0.899   |
| Corpus dominant                          | 135 (79.4)        | 26 (76.5)        | 88 (78.6)         |         |
| Treatment                                |                   |                  |                   | <0.001  |
| Endoscopic submucosal dissection         | 112 (65.9)        | 32 (94.1)        | 112 (100)         |         |
| Endoscopic mucosal resection             | 5 (2.9)           | 1 (2.9)          |                  |         |
| Argon plasma coagulation                 | 4 (2.4)           |                  |                  |         |
| Biopsy                                   | 49 (28.8)         | 1 (2.9)          |                  |         |
| Duration of follow-up (years)            | 4.0 (1.0-11.1)    | 4.0 (1.0-10.4)   | 4.1 (1.0-11.1)    |         |

Values are presented as n (%), mean±standard deviation or median (range). The status of H. pylori infection was considered positive if the result of 1 or both tests (histologic examination or rapid urease test) was positive.

LGD, low grade dysplasia; HGD, high grade dysplasia; H. pylori, Helicobacter pylori.

*Cardia, fundus or high body; *Mid body or lower body; *Antrum or angle.

cancer was higher in the HGD+EGC group than in the LGD group, with a borderline statistical significance (p=0.06, Fig. 3A). However, the incidence rate of the overall gastric neoplasm after ER did not differ between the two groups. (p=0.43 according to the log-rank test, Fig. 3B).

Table 2 compares the clinical features of 36 patients with metachronous gastric neoplasm according to the baseline tumor grade. There was no significant difference among the three groups in gender, age at metachronous recurrence, treatment modality, and interval to metachronous tumor. Most patients with metachronous neoplasm (34 of 36, 94.4%) were successfully treated by ER. Metachronous tumor size was greater in the HGD and EGC groups than in the LGD group (12.5±5.0 mm and 14.6±9.3 mm vs. 8.2±4.6 mm,
Fig. 3. Comparison of the development of metachronous neoplasm between two groups. (A) Kaplan-Meier analysis of the cumulative incidence of gastric cancer recurrence between two groups. (B) Kaplan-Meier analysis of the cumulative incidence of metachronous neoplasm between the two groups. HGD, high-grade dysplasia; EGC, early gastric cancer; LGD, low-grade dysplasia.

Table 2. Characteristics of Patients with Metachronous Gastric Neoplasm and Their Metachronous Lesions according to the Baseline Tumor Grade

| Variables                      | LGD (n=17) | HGD (n=5) | Carcinoma (n=14) | p-value |
|--------------------------------|------------|-----------|------------------|---------|
| Male gender                    | 15 (88.2)  | 5 (100.0) | 14 (100.0)       | 0.183   |
| Mean age (years)               | 59.4±11.1  | 60.3±4.3  | 63.6±10.2        | 0.432   |
| Time interval to metachronous tumor (years) | 3.0 (1.1-6.3) | 2.5 (1.1-4.7) | 3.2 (1.1-6.1) | 0.902   |
| H. pylori status               |            |           |                  |         |
| Persistent                     | 8 (47.0)   | 3 (60.0)  | 8 (53.3)         |         |
| Eradicated                     | 3 (17.6)   | 2 (40.0)  | 1 (7.1)          |         |
| Negative                       | 6 (35.3)   | 0 (0)     | 5 (35.7)         |         |
| Treatment                      |            |           |                  | 0.209   |
| Endoscopic resection           | 15 (88.2)  | 5 (100.0) | 14 (100.0)       |         |
| Surgery                        | 2 (11.8)   | 0 (0)     | 0 (0)            |         |
| Mean size (mm)                 | 8.2±4.6    | 12.5±5.0  | 14.6±9.3         | 0.042   |
| Location of primary lesion     |            |           |                  | 0.098   |
| Upper third\ast                 | 1 (5.9)    | 0 (0)     | 0 (0)            |         |
| Middle third\ast               | 7 (41.2)   | 2 (40.0)  | 3 (20.0)         |         |
| Lower third\ast                | 9 (52.9)   | 3 (60.0)  | 12 (80.0)        |         |
| Location compared with primary tumor |            |           |                  | 0.616   |
| Same third                     | 8 (47.1)   | 3 (60.0)  | 5 (35.7)         |         |
| Other third                    | 9 (52.9)   | 2 (40.0)  | 9 (64.3)         |         |
| Primary histology              |            |           |                  | 0.180   |
| Low grade dysplasia            | 13 (76.5)  | 2 (40.0)  | 7 (50.0)         |         |
| High grade dysplasia           | 0 (0)      | 0 (0)     | 0 (0)            |         |
| Early gastric cancer           | 4 (23.5)   | 3 (60.0)  | 7 (50.0)         |         |

Values are presented as n (%), mean±standard deviation or median (range).

LGD, low grade dysplasia; HGD, high grade dysplasia; H. pylori, Helicobacter pylori.
\astCardia, fundus or high body; \ast\astMid body or lower body; \ast\ast\astAntrum or angle.

p=0.042). No significant difference was found in the location and histology of metachronous neoplasm among the three groups. Metachronous tumors were in the same third location as the primary lesion in half of the total (47.1% in the LGD group, 60.0% in the HGD group, and 35.7% in the EGC group). Fig. 1 shows the patterns of metachronous cancer and treatment modalities in each group. Among the 14 cases of metachronous cancer, two EGC cases underwent gastrectomy due to undifferentiated histology. Advanced cancer was identified in one case in the HGD group and was treated with gastrectomy with additional chemotherapy due to combined liver metastasis.
Table 3. Comparison of Clinical Characteristics of Patients with Low Grade Dysplasia between the Simple Excisional Biopsy-removed Group and ESD-treated Group

| Variables               | Simple excisional biopsy-removed group (n=49) | ESD-treated group (n=112) | p-value |
|-------------------------|---------------------------------------------|---------------------------|---------|
| Age (years)             | 56.7±9.1                                    | 59.0±8.5                  | 0.161   |
| Male                    | 35 (71.4)                                   | 82 (73.2)                 | 0.847   |
| Tumor size (mm)         | 5.7±2.1                                     | 9.2±4.2                   | <0.001  |
| Follow-up duration (years) | 4.0±2.2                                    | 4.6±2.3                   | 0.148   |
| Metachronous neoplasm   | 7 (14.3)                                    | 9 (8.0)                   | 0.473   |
| Local recurrence        | 3 (6.1)                                     | 2 (1.8)                   | 0.382   |

Values are presented as n (%) or mean±standard deviation.

ESD, endoscopic submucosal dissection.

Table 4. Multivariate Cox Regression Analysis for the Cumulative Incidence of Metachronous Gastric Cancer and Neoplasm

| Variables               | Metachronous neoplasm | Metachronous cancer |
|-------------------------|-----------------------|---------------------|
|                         | HR                    | 95% CI              | p-value  | HR                    | 95% CI              | p-value  |
| Male gender             | 4.26                  | 1.00-18.34          | 0.05     | 1                     |                      | 0.26     |
| Histology               |                       | 0.85                |          |                       |                      |          |
| Low grade dysplasia     | 1                     | 0.37-3.57           |          | 3.14                  | 0.69-14.28           |          |
| High grade dysplasia    | 1.15                  | 0.37-3.57           | 0.45     | 2.37                  | 0.69-8.22            |          |
| Early gastric cancer    | 1.25                  | 0.59-2.64           |          | 1.04                  | 0.29-3.79            | 0.95     |
| Age ≥65 years           | 1.34                  | 0.63-2.84           | 0.40     | 1.26                  | 0.43-3.72            | 0.68     |
| H. pylori infection     | 1.63                  | 0.81-3.28           | 0.44     | 2.95                  | 0.78-11.12           | 0.11     |
| Multiple lesion         | 1.55                  | 0.51-4.70           | 0.35     | 0.83                  |                      |          |
| Location of primary lesion |                   |                     |          |                       |                      |          |
| Upper third\(^a\)       | 1                     |                     |          | 1                     |                      |          |
| Middle third\(^b\)      | 2.30                  | 0.29-18.60          | 1.09     | 0.13-9.32             |                      |          |
| Lower third\(^c\)       | 1.34                  | 0.18-2.94           | 0.63     | 0.14-2.87             |                      |          |

HR, hazard ratio; CI, confidence interval; H. pylori, Helicobacter pylori.
\(^a\)Cardia, fundus or high body; \(^b\)Mid body or lower body; \(^c\)Antrum or angle.

Table 3 provides the clinical characteristics and outcomes of patients with LGD comparing two sub-groups according to the treatment modality; the simple excisional biopsy-removed group vs. the ESD-treated group. Tumor size was significantly smaller in the simple excisional biopsy-removed group compared with the ESD-treated group (5.7±2.1 vs. 9.2±4.2, p<0.001). The simple excisional biopsy-removed group had higher rates of metachronous gastric neoplasm and local recurrence compared with the ESD-treated group; however, there was no statistical significance.

3. Risk factors of tumor recurrence after endoscopic treatment

We performed a multivariate Cox proportional hazard analysis to determine the risk of metachronous gastric cancer or neoplasm. Of the variables, only male gender increased the risk for metachronous gastric neoplasm (hazard ratio, 4.26; 95% confidence interval, 1.00-18.34, Table 4). And all of the metachronous gastric cancer had developed in male. The baseline histological grade of gastric neoplasia was not a significant predictor for the development of metachronous neoplasm. Older age, lesion multiplicity, H. pylori infection, and background precursor lesions (atrophy or intestinal metaplasia) were not associated with the risk of metachronous neoplasm or cancer. Among patients who were treated with ESD, en-block resection or submucosal invasion were associated with increased risk of metachronous neoplasm; however, without statistical significance.

DISCUSSION

We aimed to determine the long-term prognosis based on the clinical features of gastric neoplasm after ER with respect to the grade of dysplasia, including LGD, HGD, and EGC in a primary screening center, not in a tertiary referral center. The incidence rates of gastric neoplasm and cancer after endos-
copy treatment were not significantly different among the three groups. Consistent with our findings, a recent retrospective study has reported that histological features of gastric neoplasm did not affect the development of metachronous gastric neoplasm. However, in the following points, our study differed from this previous study. First, our study participants were relatively healthy who participated in a health-checkup program, while the previous study was conducted at a referral center in an outpatient clinic. Thus, the generalizability is greater in this study. Second, our study had a relatively long-term follow-up period with a median of 50 months, whereas in the previous study, the median follow-up period was 28 months; therefore, this study shows long-term outcomes with greater precision. Finally, in our study, we showed a comparison among three subgroups based on the primary tumor histology, separating the HGD group from invasive neoplasia, which shows long-term outcomes of three separate subgroups; in the previous study, however, only two subgroups were used.

The incidence rate of metachronous gastric neoplasm was comparable with the previous Korean study, while relatively higher compared with another previous report, as 3.4%, which were evaluated in patients with *H. pylori* eradication; this difference may be attributable to the different *H. pylori* eradication rate after ER. The preventive effect of *H. pylori* eradication for metachronous gastric cancer has not been confirmed yet. A prospective study performed in Korea has shown that *H. pylori* eradication after endoscopy treatment did not significantly decrease the incidence of metachronous cancer. Contrastingly, in a randomized controlled study, it was shown that the risk of metachronous carcinoma was reduced in patients with prophylactic *H. pylori* eradication. In fact, *H. pylori* eradication has been shown to prevent metachronous gastric cancer after ER; and as a result, it has been incorporated in a recent treatment guideline. However, *H. pylori* eradication after ER, at the moment, is not covered by the National Health Insurance system in Korea.

Despite the removal of gastric neoplasm with the surrounding mucosa by ER, most of the gastric tissues with atrophy or intestinal metaplasia may still remain. Thus, secondary lesions can frequently develop in the preserved stomach mucosa. In this study, the precursor lesions, such as intestinal metaplasia, gastric atrophy, or *H. pylori* infection, did not differ among the three groups; therefore, there may have been no significant differences in the incidences of metachronous gastric neoplasm. This finding may indicate the concept of field for carcinization, i.e., the exposure of a whole field of tissue to continuous carcinogen resulting the occurrence of cancers in a predisposed field during multistep process. However, when we combined the two groups together (HGD and EGC), the incidence of metachronous gastric cancer was higher in the combined group than in the LGD group with borderline statistical significance. This suggests that there is a difference in the premalignant potential between LGD and HGD. In fact, a large cohort study with 10 years of follow-up reported that the annual incidence of gastric cancer increased according to the severity of premalignant lesion at the initial diagnosis; 0.6% in mild-to-moderate vs. 6% in severe dysplasia. This confirms our results. In contrast to our results, the cumulative incidence of gastric cancer was not significantly different between the LGD group and the HGD+EGC group in a previous study. This difference may be attributable to the difference in the follow-up periods and discrepancies between the two study populations.

Our study demonstrated the long-term outcomes of subjects with LGD treated with simple excisional biopsy without additional ESD compared with subjects treated with ESD. There was no significant difference in the incidences of metachronous neoplasm and local recurrence between the simple excisional biopsy-removed group and the ESD-treated group. In this context, these results suggest that ‘simple excisional biopsy and follow-up’ can be cautiously applied for small LGD in selected settings, such as old age or the presence of comorbidity.

There have been no clinical guidelines for the surveillance interval and duration after endoscopic treatment. In a previous study, patients received follow-up at 2, 6, and 12 months and annually thereafter. In the present study, metachronous gastric cancer developed in a patient with EGC 5.7 years after ER and was retreated using ESD, suggesting the importance of long-term regular surveillance. In one case in the HGD group, advanced gastric cancer was found and treated with gastrectomy with additional chemotherapy due to combined liver metastasis. This indicates that careful surveillance via endoscopy should be encouraged for the dysplasia group as well as for the EGC group with the same levels of attention.

Several factors should be considered when interpreting
the results of this study. First, given the retrospective design of the study, the follow-up duration varied widely and there was a problem with the judgement of H. pylori infection status. A prospective study with a large number of participants is warranted to verify our results. Second, we did not evaluate the histologic severity of intestinal metaplasia or gastric atrophy. Further study based on the histological evaluation for the extent of intestinal metaplasia or gastric atrophy is needed to elaborate the results of this study. Third, the sample size may be too small, particularly considering that there were three different categories compared. Fourth, because the specimen obtained using a biopsy material was not representative of the entire lesion, pathological diagnosis based on forcep biopsy may have been inaccurate. Thus, patients with LGD treated with simple excisional biopsy in this study may have confounding effects for the interpretation of long-term follow-up prognosis of ER. Finally, because there is no widely accepted universal interval for a follow-up endoscopy in patients with adenoma, the period of follow-up endoscopy differed between patients with adenoma and those with carcinoma in this study, which may have influenced the quality of the study.

In conclusion, our study has demonstrated the clinical outcome and long-term prognosis of gastric neoplasm treated with ER with respect to the grade of dysplasia. The incidence rates of gastric neoplasm and cancer after endoscopy treatment were not significantly different among the three groups—LGD, HGD, and EGC. Long-term careful endoscopic surveillance should be considered in patients with adenoma and those with carcinoma in this study, which may have influenced the quality of the study.

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