

# World Journal of *Gastroenterology*

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## Retrospective Study

# Risk factors for metachronous gastric carcinoma development after endoscopic resection of gastric dysplasia: Retrospective, single-center study

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**Author contributions:** Moon HS interpreted and analyzed the data and wrote the manuscript; Sung JK designed, organized, and supervised writing of the manuscript; Kang SH and Jeong HY helped with data interpretation that was used in the current study; Yun GY and Kim JS provided input and organized the data for statistical analysis; Eun HS helped with data analysis; Song KS confirmed the pathology; all authors approved the final version of the manuscript.

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## Abstract

### AIM

To determine the gastric adenocarcinoma (GAC) occurrence rate and related factors, we evaluated the follow-up results of patients confirmed to have gastric dysplasia after endoscopic resection (ER).

### METHODS

We retrospectively analyzed the medical records, endoscopic examination records, endoscopic procedure records, and histological records of 667 cases from 641 patients who were followed-up for at least 12 mo, from among 1273 patients who were conformed to have gastric dysplasia after Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection

(ESD) of gastric mucosal lesions between January 2007 and August 2013 at the Chungnam National University Hospital.

## RESULTS

The mean follow-up period was 33.8 mo, and the median follow-up period was 29 mo (range: 12-87). During the follow-up period, the occurrence of metachronous GAC was 4.0% (27/667). The mean and median interval periods between the occurrence of metachronous GAC and endoscopic treatment of gastric dysplasia were 36.3 and 34 mo, respectively (range: 16-71). The factors related to metachronous GAC occurrence after ER for gastric dysplasia were male sex (5.3% *vs* 1.0%), open-type atrophic gastritis (9.5% *vs* 3.4%), intestinal metaplasia (6.8% *vs* 2.4%), and high-grade dysplasia (HGD; 8.4% *vs* 3.2%). Among them, male sex [OR: 5.05 (1.18-21.68), *P* = 0.029], intestinal metaplasia [OR: 2.78 (1.24-6.23), *P* = 0.013], and HGD [OR: 2.70 (1.16-6.26), *P* = 0.021] were independent related factors in multivariate analysis. Furthermore, 24 of 27 GAC cases (88.9%) occurred at sites other than the previous resection sites, and 3 (11.1%) occurred at the same site as the previous resection site.

## CONCLUSION

Male sex, intestinal metaplasia, and HGD were significantly related to the occurrence of metachronous GAC after ER of gastric dysplasia, and most GACs occurred at sites other than the previous resection sites.

**Key words:** Gastric dysplasia; Neoplasms; Second primary; Endoscopic mucosal resection; Stomach neoplasms

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**Core tip:** Gastric dysplasia is considered a premalignant lesion that can become malignant. Thus, endoscopic resection is preferred not only for the removal of these lesions but also for exact diagnosis. In our study, we investigated the relationship between the occurrence of synchronous and metachronous lesions after endoscopic treatment of gastric dysplasia and various clinical factors during the follow-up period. The incidence rates of synchronous and metachronous neoplasms after endoscopic resection of gastric dysplasia were 12.1% and 13.8%, respectively. In the multivariate analysis, age of < 60 years and intestinal metaplasia were independent risk factors of synchronous neoplasm. For metachronous neoplasm, especially metachronous gastric adenocarcinoma, independent risk factors were male sex, intestinal metaplasia, and high-grade dysplasia.

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## INTRODUCTION

Although the natural history of gastric dysplasia remains unclear, it is considered a premalignant lesion that can become malignant. Because specimens obtained by endoscopic biopsy are not representative of the entire lesion and many reports have shown histological discrepancies between such specimens and resected ones, endoscopic resection (ER) is preferred not only for the removal of these lesions but also for their exact diagnosis. Because gastric dysplasia can become malignant and poses the risk of metachronous gastric cancer, surveillance after ER is critical. Many studies have reported the short- and long-term outcomes of ER for early gastric cancer (EGC). However, the long-term results after endoscopic removal of gastric dysplasia are unclear. Therefore, we investigate the long-term outcomes and their related factors for the occurrence of gastric adenocarcinoma (GAC) after ER of gastric dysplasia.

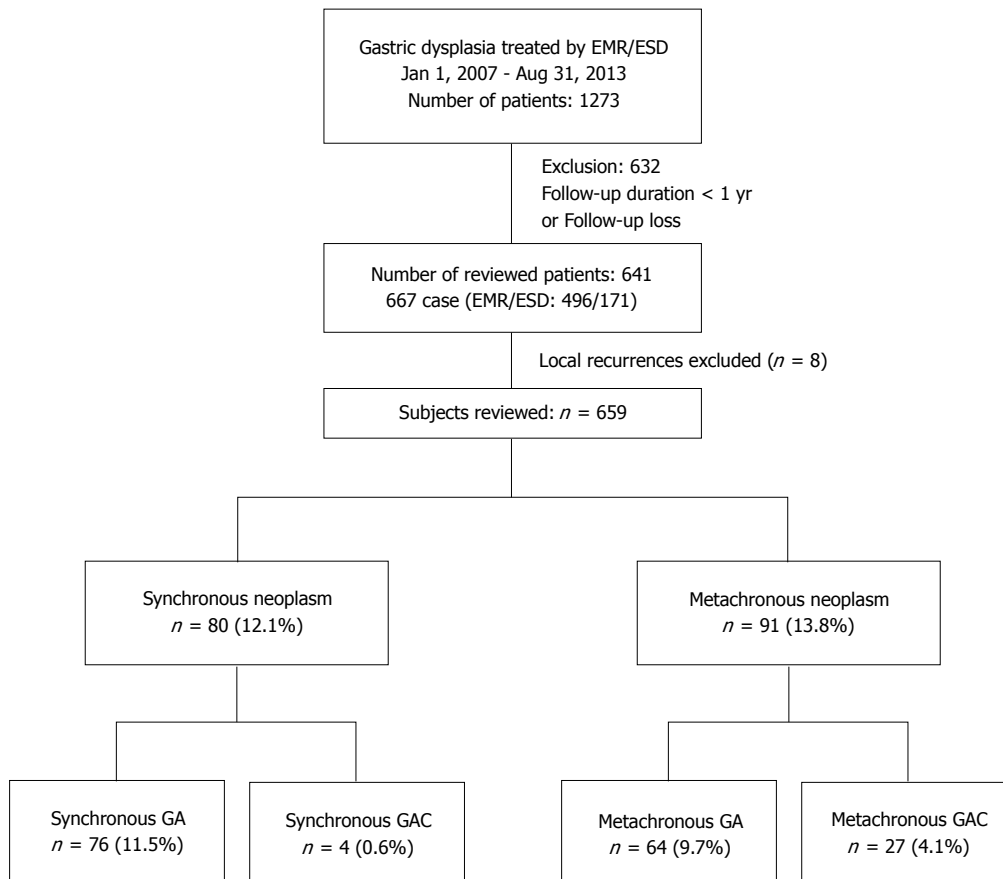
## MATERIALS AND METHODS

### Study population

This study initially included 1273 patients who were conformed to have gastric dysplasia after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of gastric mucosal lesions between January 2007 and August 2013 at the Chungnam National University Hospital, Daejeon, South Korea. Of these, 641 patients who were followed-up for at least 12 mo after endoscopic treatment were evaluated (Figure 1).

### Clinicopathological evaluation

The patients' medical records, endoscopic examination/treatment records, and histological examination results were retrospectively analyzed. The first follow-up endoscopic examination was performed between 2 and 6 mo after the endoscopic procedure. If no specific visual or pathologic abnormal lesion was observed, yearly follow-up endoscopy was performed thereafter. The occurrence rate of GAC and related factors during the follow-up period were analyzed. The lesion site was classified by dividing the gastric long axis into three sections: upper (cardia and fundus), middle (body and angle), and lower (antrum and prepylorus). The lesion size was defined as the maximum diameter of the lesion. The morphology was divided into three gross types: elevated, flat, and depressed. Cases that showed both low- and high-grade dysplasia (LGD and HGD, respectively) were classified as HGD. To determine the *Helicobacter pylori* (*H. pylori*) infection



**Figure 1 Flowchart of gastric lesion.** Initially, 667 cases were enrolled, of which 8 were local recurrences and were excluded. Finally, 659 lesions were evaluated. GA: Gastric adenoma; GAC: Gastric adenocarcinoma; EMR: Endoscopic mucosal resection; ESD: endoscopic submucosal dissection.

status, two biopsy-based tests (a histology test and a rapid urease test) and a  $^{13}\text{C}$  urea breath test were performed to determine the *H. pylori* infection status. Giemsa staining was used for a histological evaluation of *H. pylori* infection. Two specimens from the lesser curvature of the antrum and body were used in the rapid urease test (CLOtest®; Delta West, Bentley, Australia). A positive result from any of these three tests was indicative of *H. pylori* infection.

### Definitions

The gastric dysplasia grade was classified according to the Vienna classification by one specialized gastrointestinal pathologist (KS Song)<sup>[1]</sup>. We defined GAC or gastric dysplasia detected within 12 mo after ER for gastric dysplasia as synchronous lesions, and we considered mucosal lesions detected at least 12 mo after endoscopic treatment as metachronous lesions. The meaningful severity of gastric atrophy was defined as open-type atrophic gastritis by the Kimura-Takemoto classification, and the presence of intestinal metaplasia (IM) was evaluated by endoscopic examination<sup>[2,3]</sup>. Three experienced endoscopists (HS Moon, JK Sung, and HY Jeong) performed all the procedures, and all data were saved as images. The records of all the patients were reviewed retrospectively, and the severity of gastric atrophy and presence of IM in each

patient was decided after discussion among the three experts.

### Statistical analysis

Each categorical variable was analyzed using  $\chi^2$  tests. All analyses were conducted using SPSS version 19.0 (SPSS Inc., Chicago, IL, United States); *P*-values were two-sided, and *P*-values less than 0.05 were considered statistically significant. Univariate analysis was performed using  $\chi^2$  and Fisher's exact tests. Multivariate analysis was performed using all variables. The risk factors for synchronous, metachronous, and cancerous lesions were examined by multivariate analysis using the logistic regression model. The incidence of metachronous gastric lesions was calculated using the Kaplan-Meier method.

## RESULTS

### Patient characteristics

The baseline characteristics of 641 patients are shown in Table 1. The ratio of males to females was 2.4:1. The mean age of the patients was  $63.5 \pm 9.7$  years. Most of the initial lesions were located in the lower one-third of the stomach (63.9%), and 34.2% and 1.9% were located in the middle and upper thirds, respectively. Of all lesions, 69% and 31% were smaller and larger than 30 mm in size, respectively. LGD accounted for 84%

**Table 1** Baseline characteristics of patients (*n* = 641)

Patient	<i>n</i> (%)
Sex	
Male	454 (70.8)
Female	187 (29.2)
Age, years (mean ± SD)	31–88 (63.5 ± 9.7)
< 60	207 (32.3)
≥ 60	434 (67.7)
Number of resected lesions	
Single	618 (96.4)
Double	20 (3.1)
Triple	3 (0.5)
Atrophic gastritis	
Closed	570 (88.9)
Open	71 (11.1)
Intestinal metaplasia	
Absence	402 (62.7)
Presence	239 (37.3)
Site of initial lesion	
Upper	12 (1.9)
Mid	219 (34.2)
Lower	410 (63.9)
Size of initial lesion, cm	
< 3.0	442 (69.0)
≥ 3.0	199 (31.0)
Morphology of initial lesion	
Elevated	431 (67.3)
Flat	131 (20.4)
Depressed	79 (12.3)
Dysplasia grade of initial lesion	
Low	538 (84.0)
High	103 (16.0)
Helicobacter Pylori infection	
Positive	500 (78)
Negative	141 (22)

of initial confirmed lesions and HGD, for the remaining 16%. Among the patients, 570 (88.9%) and 239 (37.3%) had open-type atrophic gastritis and presence of intestinal metaplasia in the background mucosa as found endoscopically, respectively.

#### Follow-up outcomes of patients with gastric dysplasia after ER

Among the 667 cases of the 641 patients followed-up for at least 12 mo, eight lesions were local recurrences, and these were excluded from the analysis of synchronous and metachronous lesion (Figure 1). EMR and ESD were performed for 496 (74%) and 171 (26%) lesions, respectively. The overall complete resection rate was 92.3%, and it was higher in ESD cases (96.5%) than in EMR ones (90.9%). Male gender, open-type atrophic gastritis, and intestinal metaplasia were significantly different among the three groups; however, other factors were not statistically different in the baseline analysis of gastric dysplasia patients (Table 2).

#### Analysis of synchronous lesions that occurred during follow-up period

A total of 80 cases were defined as synchronous lesions. In multivariate analysis, age above 60 years (OR = 0.395, 95%CI: 0.241–0.646, *P* value = 0.000)

**Table 2** Baseline analysis of patients with gastric dysplasia *n* (%)

	Control group ( <i>n</i> = 488)	Synchronous group ( <i>n</i> = 80)	Metachronous group ( <i>n</i> = 91)	<i>P</i> value
Male gender	328 (67.2)	61 (76.2)	76 (83.5)	0.003
mean ± SD, yr	64.03 ± 9.86	61.66 ± 8.18	62.73 ± 9.96	0.131
Dysplasia				0.121
Low grade	417 (85.5)	66 (82.5)	70 (76.9)	
High grade	71 (14.5)	14 (17.5)	21 (23.1)	
En bloc resection	179 (36.7)	29 (36.2)	32 (35.2)	0.973
Intestinal metaplasia	155 (31.8)	42 (52.5)	45 (49.5)	0.000
Atrophy				0.013
Closed	445 (91.2)	67 (83.8)	75 (82.4)	
Open	43 (8.8)	13 (16.2)	16 (17.6)	
Resection method				0.439
EMR	359 (73.6)	64 (80.0)	66 (72.5)	
ESD	129 (26.4)	16 (20.0)	25 (27.5)	
Endoscopic findings				0.483
Elevated	326 (66.8)	54 (67.5)	64 (70.3)	
Flat	96 (19.7)	20 (25.0)	18 (19.8)	
Depressed	66 (13.5)	6 (7.5)	9 (9.9)	
Location				0.144
Lower	324 (66.4)	46 (57.5)	52 (57.1)	
Mid	156 (32.0)	31 (38.8)	38 (41.8)	
Upper	8 (1.6)	3 (3.8)	1 (1.1)	
mean ± SD, cm	2.12 ± 0.79	2.53 ± 1.10	2.68 ± 1.31	0.065
Helicobacter Pylori infection	385 (78.9)	67 (83.8)	66 (72.5)	0.208

and presence of IM (OR = 2.260, 95%CI: 1.377–3.707, *P* value = 0.001) showed statistically significant differences. The other groups did not show statistically significant differences when the rates were compared according to the location, size, or morphology of the lesions (Table 3).

#### Analysis of metachronous lesions that occurred during follow-up period

During the follow-up period, eight lesions recurred in the ER scar area, and these were excluded. A total of 91 lesions were finally classified as metachronous ones. Of these, 27 were pathologically diagnosed as adenocarcinoma and 64, as gastric dysplasia. In multivariate analysis, male gender (OR = 2.314, 95%CI: 1.281–4.179, *P* value = 0.005) and presence of IM (OR = 1.915; 95%CI: 1.203–3.04, *P* value = 0.006) showed statistically significant differences for metachronous lesions (Table 4). The median interval between the diagnosis of gastric dysplasia and that of the first metachronous lesion was 29.5 mo (range: 18–43 mo). The annual incidence rate of metachronous lesions per 1000 person-years was 1.26% and the cumulative 5-year incidence metachronous neoplasm after endoscopic resection of gastric dysplasia was 31% (Figure 2).

#### Analysis of metachronous gastric dysplasia during follow-up period

During the follow-up period, 27 additional cases



**Table 3 Analysis of clinical factors associated with occurrence of synchronous lesions *n* (%)**

	Control group ( <i>n</i> = 488)	Synchronous group ( <i>n</i> = 80)	Univariate analysis <i>P</i> value	Multivariate analysis		
				OR	95%CI	<i>P</i> value
Sex			0.120			
Male	328 (67.2)	61 (76.2)				
Female	160 (32.8)	19 (23.8)				
Age			0.000			0.000
≥ 60	343 (70.3)	40 (50.0)		0.395	0.241-0.646	
< 60	145 (29.7)	40 (50.0)		1.000		
Dysplasia			0.500			
Low grade	417 (85.5)	66 (82.5)				
High grade	71 (14.5)	14 (17.5)				
En bloc resection	179 (37.7)	29 (36.2)	0.941			
Intestinal metaplasia	155 (31.8)	42 (52.5)	0.001	2.260	1.377-3.707	0.001
Atrophy			0.044			0.086
Closed	445 (91.2)	67 (83.8)		1.000		
Open	43 (8.8)	13 (16.2)		1.860	0.915-3.783	
Resection method			0.269			
EMR	359 (73.6)	64 (80.0)				
ESD	129 (26.4)	16 (20.0)				
Endoscopic findings			0.231			
Elevated	326 (66.8)	54 (67.5)				
Flat	96 (19.7)	20 (25.0)				
Depressed	66 (13.5)	6 (7.5)				
Location			0.185			
Lower	324 (66.4)	46 (57.5)				
Mid	156 (32.0)	31 (38.8)				
Upper	8 (1.6)	3 (3.8)				
Size			0.295			
≤ 3	334 (68.4)	60 (75.0)				
> 3	154 (31.6)	20 (25.0)				
<i>Helicobacter Pylori</i> infection	385 (78.9)	67 (83.8)	0.371			

**Table 4 Analysis of clinical factors associated with occurrence of metachronous lesions *n* (%)**

	Control group ( <i>n</i> = 488)	Metachronous group ( <i>n</i> = 91)	Univariate analysis <i>P</i> value	Multivariate analysis		
				OR	95%CI	<i>P</i> value
Sex			0.002			0.005
Male	328 (67.2)	76 (83.5)		2.314	1.281-4.179	
Female	160 (32.8)	15 (16.5)		1.000		
Age			0.174			
≥ 60	343 (70.3)	70 (76.9)				
< 60	145 (29.7)	21 (23.1)				
Dysplasia			0.059			
Low grade	417 (85.5)	70 (76.9)				
High grade	71 (14.5)	21 (23.1)				
En bloc resection	179 (37.7)	32 (35.2)	0.813			
Intestinal metaplasia	155 (31.8)	45 (49.5)	0.002	1.915	1.203-3.049	0.006
Atrophy			0.022			0.103
Closed	445 (91.2)	75 (82.4)		1.000		
Open	43 (8.8)	16 (17.6)		1.708	0.897-3.252	
Resection method			0.897			
EMR	359 (73.6)	66 (72.5)				
ESD	129 (26.4)	25 (27.5)				
Endoscopic findings			0.665			
Elevated	326 (66.8)	64 (70.3)				
Flat	96 (19.7)	18 (19.8)				
Depressed	66 (13.5)	9 (9.9)				
Location			0.172			
Lower	324 (66.4)	52 (57.1)				
Mid	156 (32.0)	38 (41.8)				
Upper	8 (1.6)	1 (1.1)				
Size			0.394			
≤ 3	334 (68.4)	58 (63.7)				
> 3	154 (31.6)	33 (36.3)				
<i>Helicobacter Pylori</i> infection	385 (78.9)	66 (72.5)	0.210			

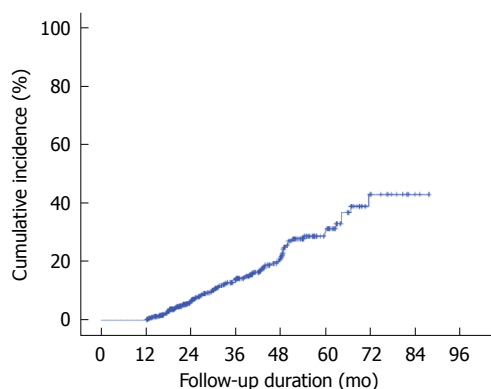


Figure 2 Cumulative incidence of metachronous neoplasm after endoscopic resection of gastric dysplasia by Kaplan-Meier analysis.

were detected within 12 mo after ER. These were considered missed synchronous lesions. Furthermore, 64 cases (9.8%) were detected after 12 mo. The mean period and median period from ER to detection of metachronous adenoma were 31.4 and 27 mo (range: 13-66 mo), respectively. In multivariate analysis, male gender (OR = 1.868, 95%CI: 0.985-3.543,  $P$  value = 0.056), IM (OR = 1.619, 95%CI: 0.947-2.767,  $P$  value = 0.078), and open-type atrophic gastritis (OR = 1.295, 95%CI: 0.589-2.846,  $P$  value = 0.520) did not show statistically significant differences for metachronous gastric dysplasia.

#### Analysis of metachronous GAC that occurred during follow-up period

In total, 31 lesions in 641 patients were pathologically diagnosed as GAC during the follow-up period. Of these, 4 and 27 were synchronous and metachronous gastric cancer, respectively. The degree of differentiation of metachronous gastric cancer was as follows: moderately differentiated cancer in 20 patients, well-differentiated cancer in 5 patients, and poorly differentiated cancer in 2 patients. The median period from ER to detection of metachronous cancer was 34 mo (range: 16-71 mo). The occurrence rate of GAC was higher in males (5.3%) than in females (1.0%), and this difference was statistically significant (OR = 5.238, 95%CI: 1.211-22.661,  $P$  value = 0.027). There was no statistically significant difference between age above (4.0%) and below (4.1%) 60 years or when the rates were compared according to the location, size, or morphology of lesions. Group who had HGD or included an HGD component had higher GAC occurrence rate (8.4% vs 3.2%) and showed a statistically significant difference (OR = 2.741, 95%CI: 1.148-6.546,  $P$  value = 0.023). When there was intestinal metaplasia in background mucosa, there was a statistically significant difference in the GAC occurrence rates (OR = 2.647, 95%CI: 1.165-6.012,  $P$  value = 0.020). Cases with open-type atrophic gastritis showed higher GAC occurrence rate than others (9.5% vs 3.4%,  $P$  value = 0.022) in univariate

analysis but not in multivariate analysis ( $P$  value = 0.188). There was small difference in occurrence rates between en bloc resection and piecemeal resection (3.7% vs 4.2%,  $P$  = 0.840). There was no statistically significant difference between EMR and ESD and between complete and incomplete resection (Table 5).

## DISCUSSION

A few studies have focused on the incidence of metachronous and synchronous lesions in patients with gastric dysplasia after ER. In a previous study, the metachronous and synchronous gastric cancer rate among patients with EGC treated by ER was reported to range from 2.7% to 14%<sup>[4-8]</sup> and 1.2% to 19.2%<sup>[5,8-10]</sup>, respectively. With recent advancements in ER for gastric lesions, most of the stomach is preserved, and the risk of developing metachronous or synchronous lesions at other sites of the remnant gastric mucosa has become a major problem. One retrospective study showed an overall incidence of 20.1% (30/149) for metachronous lesions in patients with gastric dysplasia after ER during a median period of 37.3 mo. Among these, the incidence of gastric carcinoma and dysplasia was 5.4% (8/149) and 14.8% (22/149), respectively. In addition, the incidence of synchronous lesion was 20.8% (31/149)<sup>[11]</sup>. In our study of 659 cases of 641 patients with confirmed gastric dysplasia after ER, the incidence of metachronous lesions was 13.8% (91/656) during a median follow-up period of 29 mo; among these, the incidence of metachronous gastric cancer and gastric dysplasia was 4.1% (27/656) and 9.7% (64/656), respectively. In addition, the incidence of synchronous lesions was 12.1% (80/656), most of which were gastric dysplasia.

Various predictive factors of metachronous lesion after ER have been reported for patients with EGC, including synchronous multiplicity of gastric cancer<sup>[6]</sup>, old age<sup>[6,10,12]</sup>, antrum atrophy<sup>[10]</sup>, undifferentiated histology<sup>[13]</sup> and upper location<sup>[13]</sup>, and *H. pylori* infection<sup>[14-17]</sup>. However, unlike our study, in which the focus was on gastric dysplasia, most other studies on risk factors for metachronous gastric cancer after endoscopic resection of the gastric lesion included patients with gastric adenocarcinoma. Thus, this study was designed to elucidate the independent risk factors of metachronous gastric cancer after the endoscopic removal of gastric dysplasia with a large volume. In this study, male gender, IM, and HGD were found to be independent risk factors of the development of metachronous gastric cancer after ER of gastric dysplasia.

IM is an established precancerous condition as they constitute a background for dysplasia and intestinal-type gastric cancer. According to a cohort study from China that enrolled 3306 subjects with a follow-up of 4-5 years, the OR for the progression from intestinal metaplasia to gastric cancer was

**Table 5 Analysis of risk factors associated with occurrence of metachronous carcinoma *n* (%)**

	Control group ( <i>n</i> = 488)	Metachronous carcinoma group ( <i>n</i> = 27)	Univariate analysis <i>P</i> value	Multivariate analysis		
				OR	95%CI	<i>P</i> value
Sex			0.005			0.027
Male	328 (67.2)	25 (92.6)		5.238	1.211-22.661	
Female	160 (32.8)	2 (7.4)		1.000		
Age			0.671			
≥ 60	343 (70.3)	18 (66.7)				
< 60	145 (29.7)	9 (33.3)				
Dysplasia			0.024			0.023
Low grade	417 (85.5)	18 (66.7)		1.000		
High grade	71 (14.5)	9 (33.3)		2.741	1.148-6.546	
En bloc resection	179 (37.7)	9 (33.3)	0.839			
Intestinal metaplasia	155 (31.8)	9 (33.3)	0.005	2.647	1.165-6.012	0.020
Atrophy			0.010			0.065
Closed	445 (91.2)	20 (74.1)		1.000		
Open	43 (8.8)	7 (25.9)		2.492	0.946-6.569	
Resection method			0.503			
EMR	359 (73.6)	18 (66.7)				
ESD	129 (26.4)	9 (33.3)				
Endoscopic findings			0.546			
Elevated	326 (66.8)	21 (77.8)				
Flat	96 (19.7)	3 (11.1)				
Depressed	66 (13.5)	3 (11.1)				
Location			1.000			
Lower	324 (66.4)	17 (63.0)				
Mid	156 (32.0)	9 (33.3)				
Upper	8 (1.6)	0 (0.0)				
Size			0.532			
≤ 3	334 (68.4)	17 (63.0)				
> 3	154 (31.6)	10 (37.0)				
<i>Helicobacter Pylori</i> infection	385 (78.9)	20 (74.1)	0.629			

17-29<sup>[18]</sup>. In addition, another prospective study from Japan reported that individuals with IM had at least a six-fold increase in the risk of gastric cancer<sup>[19]</sup>. However, studies that addressed the relationship between IM and metachronous lesion after ER of gastric neoplasia are scarce. Our results are consistent with those of an earlier study<sup>[20]</sup> that reported that IM was an independent risk factor of metachronous gastric neoplasia, although our study classified IM as simply positive and negative. In our study, IM was evaluated by using endoscopic examination. So the assessment of the severity of IM has some limitation. Therefore, further studies are necessary to elucidate the relationship of IM severity and the development of a metachronous lesion after ER of gastric neoplasm.

HGD is well known to be at high risk of progression to gastric cancer. The rate of malignant transformation of HGD has been reported to range from 60% to 85% over a median interval of 4 to 48 mo<sup>[21]</sup>. A recent nationwide cohort study demonstrated that HGD was associated with a 40-fold increased risk of progression to gastric cancer and that 25% of patients with HGD were diagnosed as having gastric cancer within 12 mo of follow-up<sup>[22]</sup>. Recently, one study demonstrated that the incidence of metachronous gastric cancer after ER of gastric dysplasia was similar to that after ER of EGC<sup>[23]</sup>. As only few studies have evaluated the risk factors of metachronous lesion after ER of gastric dysplasia, the association between HGD and

metachronous cancer is elusive. However, considering the above mentioned results, that is, the risk of malignant change and the similar risk of metachronous gastric cancer occurrence, HGD can be a risk factors of metachronous gastric cancer after ER of gastric dysplasia.

Male gender was also found to be a predictive factor of metachronous cancer. This result is similar to that of a previous study that suggested that male patients more frequently developed metachronous gastric cancer after surgery or ER<sup>[8,9,24]</sup>. The dominant proportion of men in our enrolled patients may have affected this result.

Some studies reported that *H. pylori* infection was associated with metachronous tumor development after ER of gastric neoplasms. One retrospective study that enrolled 184 patients with HGD and 787 patients with EGC demonstrated that *H. pylori* infection was the only independent risk factor of metachronous tumor<sup>[14]</sup>. The difference in the mean follow-up duration (37 mo) and enrolled patients (HGD and EGC) may have influenced these results. Some studies documented that *H. pylori* eradication can prevent the development of metachronous lesion after ER of gastric dysplasia<sup>[15,25,26]</sup>. In a retrospective study of 1872 patients with gastric dysplasia who underwent ER, the cumulative incidence of metachronous tumor was significantly lower in the *H. pylori*-eradicated group than in the *H. pylori*-persistent group<sup>[25]</sup>. Unlike this study, our study did

not focus on whether *H. pylori* eradication can prevent the development of metachronous tumor after ER. The effect of *H. pylori* eradication on the progression of gastric dysplasia is uncertain so far. However, *H. pylori* eradication may decrease the incidence of metachronous lesions. Currently some guideline recommend *H. pylori* eradication for patients with previous dysplasia after ER<sup>[27,28]</sup>.

Optimal surveillance strategies, including the follow-up period and interval after ER of gastric dysplasia, have not yet been established. and no population with high risk of developing metachronous neoplasms has been identified. Previous studies of early gastric cancer after ER have shown that the median interval between primary ER and diagnosis of metachronous lesion was 30-36 mo<sup>[7,10,12]</sup>. In this study, surveillance esophagogastroduodenoscopy was performed at least once a year after ER of gastric dysplasia. The median time to development of metachronous tumors was 29 mo (range, 12-71 mo). In our study, aggressive carcinoma was not detected within follow-up period, and all diagnosed metachronous gastric cancers were resected endoscopically. Based on these findings, we recommend that yearly surveillance after ER of gastric dysplasia is adequate for high-risk patient groups (male patients and those with high-grade dysplasia and intestinal metaplasia). Meticulous endoscopic follow-up after ER in patients with gastric dysplasia can result in early diagnosis of gastric cancer.

This study has some limitations. First, it was a single-center, retrospective study. Second, the severity of atrophy and presence of IM were graded based on endoscopic findings instead of pathological results. Third, the number of patients enrolled in this study was relatively small, and the follow-up duration was relatively short. Finally, about half of the patients were not followed up, and the occurrence rates of synchronous and metachronous lesions could be underestimated.

In conclusion, this study showed that the incidence rates of synchronous and metachronous neoplasms after ER of gastric dysplasia were 12.1% and 13.8%, respectively. Of these cases, 4.1% are metachronous GAC. The median detection period of metachronous gastric cancer after ER was 31 mo. Male gender, IM, and HGD were independent risk factors of metachronous GAC after ER of gastric dysplasia. Therefore, careful endoscopic surveillance should be performed in patients with IM and HGD after ER of gastric dysplasia.

## COMMENTS

### Background

Gastric dysplasia is known as a neoplastic lesion and precursor of gastric adenocarcinoma. Although the natural course of gastric dysplasia is unclear, considerable evidence suggests that patients with gastric dysplasia are at increased risk of gastric cancer. Therefore, endoscopic mucosal resection or endoscopic submucosal dissection is routinely performed for resection of the

premalignant lesion. After resection of gastric dysplasia, gastric adenocarcinoma can be detected during the follow-up period. However, few studies have been conducted regarding factors related to the development of gastric cancer. Therefore, they evaluated the results during follow-up in patients who had been confirmed as having gastric dysplasia after endoscopic resection.

### Research frontiers

Studies regarding long-term results of endoscopic removal of gastric dysplasia are scarce. Many studies have reported the short- and long-term outcomes of endoscopic treatment for early gastric cancer. The results of this study contribute to clarifying long-term outcomes and the factors related to the development of gastric adenocarcinoma (GAC) after endoscopic resection (ER) of gastric dysplasia.

### Innovations and breakthroughs

In this study, the incidences of synchronous and metachronous neoplasms after endoscopic resection of gastric dysplasia were 12.1% and 13.8%, respectively; in particular, that of metachronous GAC was 4.1%, and male gender, intestinal metaplasia, and high-grade dysplasia were independent risk factors of metachronous GAC. This emphasizes that careful endoscopic surveillance should be performed after ER of gastric dysplasia.

### Applications

This study suggests that yearly and meticulous endoscopic surveillance after ER of gastric dysplasia is adequate for high-risk patients (male patients and those with the presence of high-grade dysplasia and intestinal metaplasia).

### Terminology

Dysplasia: With reference to the gastrointestinal system, defined as the presence of histologically unequivocal neoplastic epithelium without evidence of tissue invasion. Synchronous: Defined as secondary gastric neoplasms found in another site and within 1 year of endoscopic treatment. Metachronous: Defined as new gastric neoplasms occurring in different areas from that of the initial lesion at least 1 year after ER.

### Peer-review

The author of this paper evaluated the incidence and related risk factors of synchronous and metachronous neoplasms after endoscopic resection of gastric dysplasia. Male gender, underlying intestinal metaplasia, and histopathologically confirmed high-grade dysplasia after endoscopic resection were independent risk factors of metachronous gastric cancer; and further clinical trials in a large population of gastric dysplasia patients will be valuable.

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