



Retrospective Study

Association between *Helicobacter pylori* status and metachronous gastric cancer after endoscopic resection

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Abstract

AIM

To investigate the effect of *Helicobacter pylori* (*H. pylori*) status test and *H. pylori* eradication on the occurrence of metachronous gastric cancer (MGC) after endoscopic submucosal dissection (ESD) of early gastric cancer (EGC) and risk factors of MGC.

METHODS

The authors retrospectively reviewed the medical records of 433 patients (441 lesions) who underwent ESD for EGC from January 2005 to January 2015 in Yeungnam University Hospital. Patients were categorized into two groups; the *H. pylori* tested group ($n = 257$) and the *H. pylori* non-tested group ($n = 176$) based on performance of *H. pylori* status test after ESD of EGC. The *H. pylori* tested group was further categorized into three subgroups based on *H. pylori* status; the *H. pylori*-eradicated subgroup ($n = 120$), the *H. pylori*-persistent subgroup ($n = 42$), and the *H. pylori*-negative subgroup ($n = 95$). Incidences of MGC and risk factors of MGC were identified.

RESULTS

Median follow-up duration after ESD was 30.00 mo (range, 6-107 mo). Total 15 patients developed MGC during follow-up. MGC developed in 11 patients of the *H. pylori* tested group (7 in the *H. pylori*-negative subgroup, 3 in the *H. pylori*-eradicated subgroup, and 1 in the *H. pylori*-persistent subgroup) and 4 patients

of the *H. pylori* non-tested group ($P > 0.05$). The risk factors of MGC were endoscopic mucosal atrophy in the *H. pylori* tested group and intestinal metaplasia in all patients.

CONCLUSION

H. pylori eradication and *H. pylori* status test seems to have no preventive effect on the development of MGC after ESD for EGC. The risk factors of MGC development were endoscopic mucosal atrophy in the *H. pylori* tested group alone and intestinal metaplasia in all patients.

Key words: Metachronous gastric cancer; Endoscopic submucosal dissection; *Helicobacter pylori*

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Core tip: This is a retrospective study to evaluate the effect of *Helicobacter pylori* (*H. pylori*) status test and *H. pylori* eradication on the occurrence of metachronous gastric cancer (MGC) after endoscopic submucosal dissection (ESD) of early gastric cancer (EGC) and risk factors of MGC. *H. pylori* status test and *H. pylori* eradication seems to have no preventive effect on the occurrence of MGC after ESD for EGC. The risk factors of MGC were endoscopic gastric mucosal atrophy in *H. pylori* tested group alone and intestinal metaplasia in all patients.

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INTRODUCTION

Endoscopic resection (ER) including endoscopic mucosal resection and endoscopic submucosal dissection (ESD) is a recognized as one of treatment options for curative resection of early gastric cancer (EGC) without simultaneous concomitant lymph node metastasis^[1-4]. Unlike surgery of EGC, ER preserves most part of the stomach and this leads to increased risk of metachronous gastric cancer (MGC) development in residual gastric mucosa^[5]. As more EGCs are treated with ER recently, identifying risk factors of MGC development after ER of EGC is important.

Helicobacter pylori (*H. pylori*) infection is related to the development of gastritis, atrophy, intestinal metaplasia, dysplasia, and gastric cancer^[6-9]. Among dietary, environmental, and genetic risk factors of gastric cancer, *H. pylori* is classified as a Group 1 or definite carcinogen for gastric cancer by the World Health Organization^[10]. In previous reports, the odds

for development of gastric cancer reported to increase by 2-4 folds in the patients with *H. pylori* infection^[11,12].

The effect of *H. pylori* eradication on development of MGC after ER of EGC is still on debate. A study of 132 patients who underwent ER for EGC and showed positive *H. pylori* serologic test demonstrated that *H. pylori* eradication inhibited the growth of new gastric cancer^[13] and a retrospective study of 283 patients with *H. pylori* infection at time of ESD for EGC showed that failure of *H. pylori* eradication was a risk factor of MGC development^[5]. However, a study of 1258 patients who underwent ESD for EGC reported that the incidence rate of MGC was not significantly different between patients with or without *H. pylori* eradication^[14] and a retrospective study of 268 patients with a 5-year follow-up reported that *H. pylori* eradication after ER for EGC did not significantly reduced the incidence of MGC^[15]. Studies about the effect of *H. pylori* status test on development of MGC after ER of EGC has been scarce.

The aims of this study were to investigate the effect of *H. pylori* status test and *H. pylori* eradication on the occurrence of MGC after ESD of EGC and risk factors of MGC.

MATERIALS AND METHODS

Patients

The medical records of 599 patients with 611 lesions who underwent ESD for EGC from January 2005 to January 2015 at Yeungnam university hospital were retrospectively reviewed. Exclusion criteria of the present study were as follows: additional gastrectomy due to a non-curative ESD of EGC and short-term follow-up duration (< 6 mo) and a total of 166 patients with 170 lesions were excluded from the present study. Finally, 433 patients with 441 lesions were included for analysis. Baseline clinical characteristics of the patients, characteristics and histology findings of EGC, performance of *H. pylori* status test and *H. pylori* eradication and occurrence of MGC were analyzed. Institutional review board approval was obtained for this study (2016-06-035).

H. pylori status and follow-up

Patients were divided into two groups; the *H. pylori* tested group ($n = 257$) and the *H. pylori* non-tested group ($n = 176$) based on performance of *H. pylori* status test after ESD of EGC. Patients in the *H. pylori* tested group were further divided into three subgroups; the *H. pylori* negative subgroup, the *H. pylori* eradicated subgroup, and the *H. pylori* persistent subgroup (Figure 1).

Among patients with positive *H. pylori* test results, patients who agreed to treat *H. pylori* infection received *H. pylori* eradication. The regimen for first-line *H. pylori* treatment was triple therapy with amoxicillin 1000 mg, clarithromycin 500 mg, and a proton-pump inhibitor (pantoprazole 40 mg, eomeprazole 40 mg, lansoprazole 30 mg or rabeprazole 20 mg)

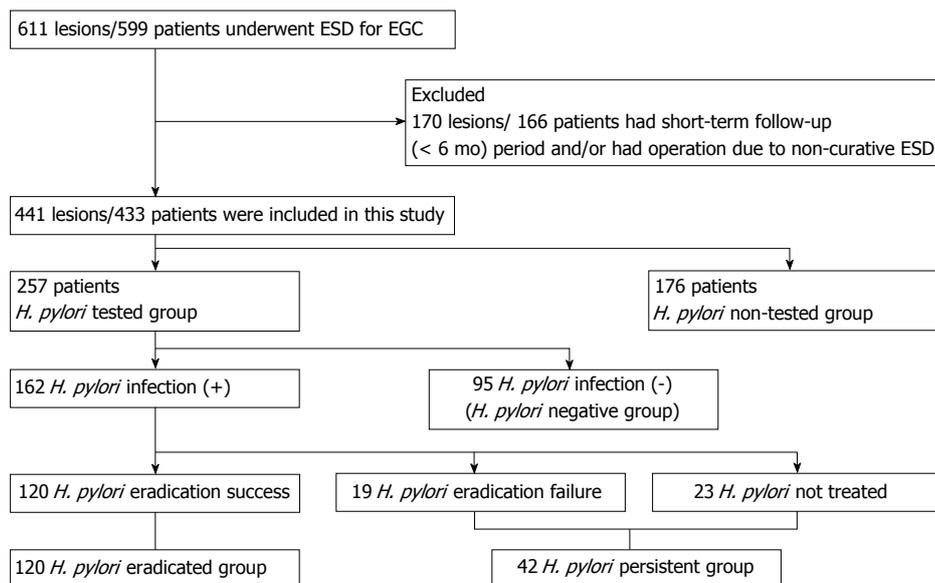


Figure 1 Study flowchart. EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*.

all twice daily for a week. The regimen for second-line *H. pylori* treatment was a quadruple therapy with metronidazole 500 mg (3 times daily), tetracycline 500 mg (4 times daily), tripotassium dicitrato bismuthate 300 mg (4 times daily), and a proton-pump inhibitor (twice daily) for 10–14 d. Eradication was confirmed by histology or rapid urase test at scheduled esophagogastroduodenoscopy (EGD) follow-up after ESD or urea breathing test. After ESD, scheduled EGD was performed at 2 or 3, 6, and 12 mo, and annually thereafter.

The presence of gastric mucosal atrophy was assessed through EGD and presence of intestinal metaplasia through histology. MGC was defined as the development of new gastric cancer at a previously uninvolved site in the stomach after the 6 mo following ESD. MGC was confirmed by histology of biopsy specimens. Incidences of MGC was compared according to performance of *H. pylori* status test and among the *H. pylori* eradicated, persistent and negative group and risk factors of MGC were analyzed.

Statistical analysis

Results are presented as means and standard deviations or as medians and ranges. The χ^2 or Fisher's exact test and one-way analysis of variance test or the Student's *t*-test were used to compare categorical and continuous variables, respectively. The log-rank test was used for to compare group incidence rates. Univariate and multivariate Cox proportional hazard regression analyses were used to identify independent risk factors associated with MGC development. Covariates with *P* values of < 0.05 by univariate analyses were entered into multivariate analysis. Statistical analyses of the data were performed using SPSS 20 (IBM SPSS, Chicago, IL, United States). Statistical significance was accepted for *P* values < 0.05.

RESULTS

Baseline characteristics of the patients

Mean age of the 433 patients included in the present study was 67.02 years and 325 (75.1%) patients were male and 108 (24.9%), female. Median follow-up duration after ESD of EGC was 30.00 mo (range, 6–107 mo).

Among 257 patients of the *H. pylori* tested group, 162 (63.0%) patients showed positive result for *H. pylori* test and 95 (37.0%) patients, negative. Of these 162 patients with positive result of *H. pylori* test, *H. pylori* eradication was done in 139 patients and eradication was successful in 120 (86.3%) patients. Ninety-five patients without *H. pylori* infection were classified as the *H. pylori*-negative subgroup, 120 patients with successful *H. pylori* eradication as the *H. pylori*-eradicated subgroup, and 42 patients (19 patients in whom *H. pylori* eradication failed and 23 patients not treated for *H. pylori* infection) as the *H. pylori*-persistent subgroup (Figure 1). The mean age of *H. pylori* tested group was 66.61 years and 189 (73.5%) patients were male. Patients in the *H. pylori*-eradicated subgroup were significantly younger than patients in the *H. pylori*-negative and *H. pylori*-persistent subgroups (*P* < 0.05). The mean follow-up duration was not significantly different between three subgroups (*P* > 0.05). Endoscopic mucosal atrophy and intestinal metaplasia were significantly more prevalent in the *H. pylori*-negative subgroup than the other two subgroups (*P* < 0.05). The location and macroscopic type of primary gastric cancer were not significantly different between three subgroups (*P* > 0.05). The *H. pylori*-persistent subgroup had significantly less differentiated cancers than other two subgroups (*P* = 0.032) (Table 1).

The mean age and follow-up duration were not

Table 1 Baseline characteristics of patients in the *Helicobacter pylori* tested group *n* (%)

	<i>H. pylori</i> negative group (<i>n</i> = 95)	<i>H. pylori</i> persistent group (<i>n</i> = 42)	<i>H. pylori</i> eradicated group (<i>n</i> = 120)	<i>P</i> value
Sex				
Male	74 (77.9)	29 (69.0)	86 (71.7)	0.454
Female	21 (22.1)	13 (31.0)	34 (28.3)	
Age, mean (SD)	68.65 (8.86)	67.31 (9.12)	64.76 (10.10)	0.011
Follow-up period (mo), mean (SD)	36.18 (\pm 26.74)	33.29 (\pm 25.93)	32.78 (\pm 23.72)	0.149
Endoscopic mucosal atrophy	50 (52.6)	8 (19.0)	25 (20.8)	< 0.001
Intestinal metaplasia	63 (66.3)	18 (42.9)	32 (26.7)	< 0.001
Location of primary cancer				
Upper	10 (10.5)	5 (11.9)	10 (8.3)	0.577
Middle	36 (37.9)	14 (33.3)	35 (29.2)	
Lower	49 (51.6)	23 (54.8)	75 (62.5)	
Macroscopic type of primary cancer				
Elevated	40 (42.1)	122 (8.6)	57 (47.5)	0.177
Flat	13 (13.7)	5 (11.9)	9 (7.5)	
Depressed	42 (37.0)	25 (59.5)	54 (45.0)	
Diameter of primary cancer (cm), mean (SD)	14.24 (7.31)	13.83 (6.22)	13.67 (6.90)	0.978
Histology of primary cancer				
Differentiated	93 (97.9)	38 (90.5)	118 (98.3)	0.032
Undifferentiated	2 (2.1)	4 (9.5)	2 (1.7)	
ESD criteria				
Absolute	73 (76.8)	33 (78.6)	95 (79.2)	0.636
Expanded	18 (18.9)	5 (11.9)	19 (15.8)	
Beyond expanded	4 (4.2)	4 (9.5)	6 (5.0)	
Depth of primary cancer				
Mucosa	89 (93.7)	40 (95.2)	111 (92.5)	0.819
Submucosa	6 (6.3)	2 (4.8)	9 (7.5)	
Metachronous cancer recurrence	7 (7.4)	1 (2.4)	3 (2.5)	0.173

ESD: Endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*.

significantly different between the *H. pylori* tested and the *H. pylori* non-tested groups ($P > 0.05$). Endoscopic mucosal atrophy and intestinal metaplasia was significantly more frequent in the *H. pylori* tested group than in the *H. pylori* non-tested group, and location of primary gastric cancer location was significantly lower in the *H. pylori* tested group than the *H. pylori* non-tested group ($P < 0.05$). In addition, the *H. pylori* non-tested group had more elevated lesions than the *H. pylori* tested group and the *H. pylori* tested group had more depressed lesions than the *H. pylori* non-tested group ($P < 0.05$) (Table 2).

Development of MGC according to *H. pylori* status

Among total 433 patients, MGC developed in 15 (3.5%) patients; 11 (4.3%) patients in the *H. pylori* tested group and 4 (2.3%) in the *H. pylori* non-tested group without significant difference ($P = 0.262$) (Table 2).

Among 11 patients who developed MGC in the *H. pylori* tested group, MGC developed in 7 (7.4%) patients of the *H. pylori*-negative subgroup, 3 (2.5%) patients of the *H. pylori*-eradicated subgroup, and 1 (2.4%) patient of the *H. pylori*-persistent subgroup. Although the incidence of MGC was higher in the *H. pylori*-negative subgroup than other two subgroups, statistical significance was not found among the three subgroups ($P = 0.173$) (Table 1).

Characteristics of patients with MGC

Mean age of patients with MGC was 68.93 years and all patients with MGC were male. No significant differences were observed between MGC group and non-MGC group in terms of age, primary cancer location, and primary lesion size ($P > 0.05$), and mean follow-up duration was not significantly different between two groups ($P = 0.752$). Endoscopic mucosal atrophy and intestinal metaplasia were significantly more prevalent in patients with MGC than without ($P < 0.05$) (Table 3).

In the *H. pylori* tested group, age, primary cancer location, and lesion size were not significantly different between patients with or without MGC and follow-up duration was similar between two groups (33.72 ± 23.64 vs 34.13 ± 25.30 , $P = 0.997$). The patient with MGC showed higher proportion of negative *H. pylori* status than without (63.6% vs 35.8%, $P = 0.061$). However, endoscopic mucosal atrophy and intestinal metaplasia were observed significantly more in patients with MGC than without (72.7% vs 30.5%, $P = 0.003$ and 81.8% vs 42.3%, $P = 0.010$) (Table 4).

Factors associated with the development of MGC

In the *H. pylori* test group, endoscopic mucosal atrophy and intestinal metaplasia were found to be significantly associated with the development of MGC by univariate analysis ($P < 0.05$). Multivariate Cox proportional

Table 2 Baseline characteristics of patients according to performance of *Helicobacter pylori* status test *n* (%)

	<i>H. pylori</i> tested group (<i>n</i> = 257)	<i>H. pylori</i> non-tested group (<i>n</i> = 176)	<i>P</i> value
Sex			
Male	189 (73.5)	136 (77.3)	0.378
Female	68 (26.5)	40 (22.7)	
Age, mean (SD)	66.61 (9.63)	67.60 (10.03)	0.303
Follow-up period (mo), mean (SD)	34.12 (25.19)	33.31 (18.11)	0.699
Endoscopic mucosal atrophy	83 (32.3)	12 (6.8)	< 0.001
Intestinal metaplasia	113 (44.0)	14 (8.0)	< 0.001
Location of primary cancer			
Upper	25 (9.7)	12 (6.8)	
Middle	85 (33.1)	37 (21.0)	0.006
Lower	147 (57.2)	127 (72.2)	
Macroscopic type of primary cancer			
Elevated	109 (42.4)	95 (54.0)	
Flat	27 (10.5)	24 (13.6)	0.009
Depressed	121 (47.1)	57 (32.4)	
Diameter of primary cancer (cm), mean (SD)	13.91 (6.93)	14.30 (5.74)	0.540
Histology of primary cancer			
Differentiated	249 (96.9)	171 (97.2)	
Undifferentiated	8 (3.1)	5 (2.8)	0.871
ESD criteria			
Absolute	201 (78.2)	142 (80.7)	0.234
Expanded	42 (16.3)	20 (11.4)	
Beyond expanded	14 (5.4)	14 (8.0)	
Depth of primary cancer			
Mucosa	240 (93.4)	161 (91.5)	0.456
Submucosa	17 (6.6)	15 (8.5)	
Metachronous cancer recurrence	11 (4.3)	4 (2.3)	0.262

ESD: Endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*.**Table 3** Comparisons of clinical characteristics between patients with or without metachronous gastric cancer in all patients *n* (%)

	Non-metachronous gastric cancer group (<i>n</i> = 418)	Metachronous gastric cancer group (<i>n</i> = 15)	<i>P</i> value
Sex			
Male	310 (74.2)	15 (100)	0.028
Female	108 (25.8)	0 (0)	
Age, mean (SD)	66.95 (9.82)	68.93 (9.35)	0.441
Location of primary cancer			
Upper	35 (8.4)	2 (13.3)	0.163
Middle	115 (27.5)	7 (46.7)	
Lower	268 (64.1)	6 (40.0)	
Lesion size (cm), mean (SD)	14.01 (6.10)	15.60 (13.48)	0.350
Endoscopic mucosal atrophy	87 (20.8)	8 (53.3)	0.003
Intestinal metaplasia	117 (28.0)	10 (66.7)	0.001
Histology of undifferentiated type	12 (2.9)	1 (6.7)	0.397
SM invasion	31 (7.4)	1 (6.7)	0.913
Non-performance of <i>H. pylori</i> status test	172 (41.1)	4 (26.7)	0.262
Follow-up period (mo), mean period (SD)	33.72 (22.58)	35.60 (22.68)	0.752

SM: Submucosa; *H. pylori*: *Helicobacter pylori*.

hazard regression analysis revealed an association with MGC development only for endoscopic mucosal atrophy (HR = 6.080, *P* = 0.009) (Table 5).

In all patients, endoscopic mucosal atrophy and intestinal metaplasia were significantly associated with MGC development in univariate analysis and multivariate Cox proportional hazard regression analysis showed an association between intestinal metaplasia and MGC development (HR = 4.67, *P* = 0.006) (Table 6).

DISCUSSION

In the present study, 15 (3.5%) of the 433 patients developed MGC after ESD for EGC and this result was comparable with previous reports^[16,17]. MGC occurs more frequently after ER for EGC than surgery (2.5%-14% vs 1.8%-5%)^[16-19]. This increased risk of MGC after ER for EGC can be partly explained by higher proportion of salvaged stomach in ER than

Table 4 Comparisons of the clinical characteristics of patients with or without metachronous gastric cancer in the *Helicobacter pylori* tested group *n* (%)

	Non-metachronous gastric cancer group (<i>n</i> = 246)	Metachronous gastric cancer group (<i>n</i> = 11)	<i>P</i> value
Sex			
Male	178 (72.4)	11 (100)	0.042
Female	68 (29.6)	0 (0)	
Age, mean (SD)	66.44 (9.66)	70.45 (8.52)	0.177
Location of primary cancer			
Upper	24 (9.8)	1 (9.1)	0.290
Middle	79 (32.1)	6 (54.5)	
Lower	143 (58.1)	4 (36.4)	
Lesion size (cm), mean (SD)	13.75 (6.32)	17.36 (15.45)	0.458
Endoscopic mucosal atrophy	75 (30.5)	8 (72.7)	0.003
Intestinal metaplasia	104 (42.3)	9 (81.8)	0.010
Histology of undifferentiated type	8 (3.3)	0 (0)	0.543
SM invasion	16 (6.5)	1 (9.1)	0.736
Persistent <i>H. pylori</i> infection	41 (16.7)	1 (9.1)	0.173
<i>H. pylori</i> negative	88 (35.8)	7 (63.6)	0.061
Follow-up period (mo), mean (SD)	34.13 (25.30)	33.72 (23.64)	0.958

SM: Submucosa; *H. pylori*: *Helicobacter pylori*.**Table 5** Results of univariate and multivariate analysis for factors associated with the development of metachronous gastric cancer in the *Helicobacter pylori* tested group

	Univariate analysis			Multivariate analysis		
	HR	95%CI	<i>P</i> value	HR	95%CI	<i>P</i> value
Age ≥ 65 yr	1.736	0.449-6.705	0.424			
Endoscopic mucosal atrophy	6.080	1.569-23.556	0.009	6.080	1.569-23.556	0.009
Intestinal metaplasia	6.144	1.300-29.033	0.022	2.654	0.400-17.621	0.312
Histology of undifferentiated type	0.000	0.000	0.999			
SM invasion	1.437	0.173-11.942	0.737			
<i>H. pylori</i> negative	3.142	0.895-11.031	0.074	1.638	0.426-6.299	0.473
<i>H. pylori</i> eradication	0.413	0.107-1.595	0.200			

SM: Submucosa; *H. pylori*: *Helicobacter pylori*.**Table 6** Results of univariate and multivariate analysis for factors associated with the development of metachronous gastric cancer in all patients

	Univariate analysis			Multivariate analysis		
	HR	95%CI	<i>P</i> value	HR	95%CI	<i>P</i> value
Age ≥ 65 yr	1.317	0.442-3.923	0.620			
Endoscopic mucosal atrophy	4.348	1.535-12.320	0.006	1.966	0.526-7.351	0.315
Intestinal metaplasia	5.145	1.722-15.373	0.003	5.145	1.722-15.373	0.003
Histology of undifferentiated type	2.417	0.293-19.902	0.412			
SM invasion	0.892	0.113-7.007	0.913			
<i>H. pylori</i> non-tested	0.520	0.163-1.660	0.270			

SM: Submucosa; *H. pylori*: *Helicobacter pylori*.

surgery. The mean duration of MGC development from ESD of EGC was 35.6 mo and 3 patients developed MGC after 5 years from initial ESD of EGC. A retrospective study of 1526 patients who underwent ESD for EGC reported that 5-year, 7-year, and 10-year cumulative incidence functions of MGC were 9.5%, 13.1%, and 22.7%, respectively^[20]. Meticulous examination at surveillance EGD is needed in patients who underwent ER for EGC and EGD should be done with schedule. Further studies are needed to find optimal schedule for

surveillance EGD after ER of EGC.

The chronic inflammation of stomach induced by *H. pylori* infection may lead to mucosal atrophy, intestinal metaplasia, and dysplasia, and risk of developing gastric cancer is increased in patients exhibiting such histologic changes of stomach^[21,22]. An animal study has reported that *H. pylori* eradication decreased polyp formation, inflammatory cell infiltration, and cellular proliferation in the gastric mucosa and suggested that *H. pylori* eradication could diminish mucosal alterations

related to gastric carcinogenesis^[23]. However, the preventative effect of *H. pylori* eradication on MGC development after ESD for EGC is still on debate. In the present study, the incidence of MGC after ESD of EGC was not significantly different between the *H. pylori*-negative subgroup, the *H. pylori*-eradicated subgroup, and the *H. pylori*-persistent subgroups and *H. pylori* eradication had no preventive effect on the development of MGC after ESD of EGC. However, the *H. pylori*-negative subgroup showed higher tendency towards development of MGC after ESD of EGC than other two subgroups without statistical significance and this might be due to significantly higher proportion of endoscopic mucosal atrophy and intestinal metaplasia in the *H. pylori*-negative subgroup than other two subgroups. The higher proportion of patients with intestinal metaplasia in the *H. pylori*-negative subgroup might have led to false negative result in the *H. pylori* status test.

In the present study, the development of MGC was compared according to performance of *H. pylori* status test and no significant difference in the development of MGC after ESD of EGC was observed between two groups during follow-up. As *H. pylori* status test and *H. pylori* eradication failed to show preventive effect on development of MGC after ESD of EGC in the present study, further large scaled prospective studies are needed to clarify the effect of *H. pylori* status test and *H. pylori* eradication on MGC development in patients who underwent ESD for EGC.

The mucosal atrophy of stomach has been previously reported to contribute to the development of MGC^[15]. A study of 100 patients who underwent ESD for EGC reported that the frequency of severe atrophy assessed by histology was higher in the group that developed cancer compared to the group that did not and severity of atrophy was the only independent risk factor of MGC development after *H. pylori* eradication^[24]. In the present study, endoscopic mucosal atrophy and intestinal metaplasia were observed more frequently in patients with MGC than in those without. Furthermore, multivariate analysis showed that endoscopic mucosal atrophy in the *H. pylori* tested group and intestinal metaplasia in all patients as a risk factor of MGC development after ESD of EGC.

The effect of *H. pylori* eradication on improvement of mucosal atrophy remains unclear in previous studies^[25-28]. A study of 544 patients with EGC reported the preventive effect of *H. pylori* eradication on development of MGC after ER of EGC even in patients with corpus atrophy^[29]. However, a large-scale, randomized, and controlled study about 1630 healthy carriers of *H. pylori* infection in China reported that the *H. pylori* carriers with precancerous state defined as presence of mucosal atrophy, intestinal metaplasia, or dysplasia had no preventive effect of *H. pylori* eradication on development of gastric cancer^[30]. The ineffectiveness of *H. pylori* eradication on MGC development after ESD of EGC in the present study

might have been due to irreversible mucosal atrophic change. Further studies to clarify the effect of *H. pylori* eradication on MGC development according to status of gastric mucosa is needed.

In the present study, all patients who developed MGC were male. A previous study reported that male gender was one of risk factors for MGC development of ESD of EGC^[20]. However, male gender was not found as a risk factor of MGC in the present study and further study with longer follow up duration is needed to clarify the effect of gender on development of MGC after ESD of EGC.

The present study has several limitations. First, its retrospective nature study makes selection bias inevitable, as was reflected by differences in the baseline characteristics of patients including atrophy and intestinal metaplasia status. Second, relatively small patients of MGC were included for the analysis, and if more patients with MGC had been included, it is possible that *H. pylori* eradication might have been found to influence MGC development. Third, determination of *H. pylori* infection status was inadequate, and thus, false negative and positive results were possibly included. Fourth, we did not examine other causes of mucosal atrophy.

In conclusion, *H. pylori* eradication and *H. pylori* status test seems to have no preventive effect on the development of MGC after ESD for EGC. The risk factors of MGC development after ESD of EGC were gastric mucosal atrophy in *H. pylori* tested group and intestinal metaplasia in all patients.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) infection is related to the development of gastritis, atrophy, intestinal metaplasia, dysplasia, and gastric cancer. The odds for development of gastric cancer reported to increase by 2-4 folds in the patients with *H. pylori* infection in previous studies. The effect of *H. pylori* eradication on development of metachronous gastric cancer (MGC) after endoscopic resection (ER) of early gastric cancer (EGC) is still on debate. Studies about the effect of *H. pylori* status test on development of MGC after ER of EGC has been scarce. In this study, we evaluated the effect of *H. pylori* status test and *H. pylori* eradication on the occurrence of MGC after endoscopic submucosal dissection (ESD) of EGC and risk factors of MGC.

Research frontiers

Studies about the preventive role of *H. pylori* eradication in the development of MGC after ER of EGC showed conflicting results.

Innovations and breakthroughs

In this study, *H. pylori* status test and *H. pylori* eradication seems to have no preventive effect on the development of MGC after ESD for EGC. The risk factors of MGC development were endoscopic gastric mucosal atrophy in *H. pylori* tested group alone and intestinal metaplasia in all patients.

Applications

Due to retrospective nature of the study, further prospective studies to clarify the effect of *H. pylori* status test and *H. pylori* eradication on the occurrence of MGC after ESD of EGC and risk factors of MGC are needed.

Terminology

Early gastric cancer: An adenocarcinoma that is restricted to the mucosa or submucosa of stomach, irrespective of lymph node metastasis.

Peer-review

To provide the comments from peer reviewers that most represent the characteristics, values and significance of the article, and allow the readers to have an objective point of view toward the article.

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