

# Correlation between healing type of lesion and recurrence in gastric neoplastic lesions after endoscopic submucosal dissection

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**Cite this article as:** Cha JH, Jang JS. Correlation between healing type of lesion and recurrence in gastric neoplastic lesions after endoscopic submucosal dissection. *Turk J Gastroenterol* 2020; 31(1): 36-41.

## ABSTRACT

**Background/Aims:** To date, there are few reports on the clinical association between healing pattern of lesion and local recurrence after endoscopic resection (ER). We examined the risk factors associated with local recurrence after endoscopic submucosal dissection (ESD) and the correlation between healing type of lesion and recurrence.

**Materials and Methods:** We retrospectively analyzed medical records of 293 patients who underwent ESD of early gastric cancer or gastric adenoma between April 2010 and January 2012. We analyzed the relationship among factors such as age, location of lesion, size, pathologic diagnosis, presence of *Helicobacter pylori* (*H. pylori*), and healing types of ulcers in patients with local recurrence through follow-up endoscopic surveillance (1, 6, and 12 months after ESD).

**Results:** We analyzed 141 patients except for patients who had not undergone surveillance endoscopy, *H. pylori* test, and ambiguous healing patterns. There were no significant correlations between local recurrences concerning sex, age, tumor size, location, and pathologic diagnosis. When the healing type of the ulcer was divided into hypertrophic polypoid type (9 cases (6.4%)), scar type (122 cases (86.5%)), and nodular type (10 cases (7.1%)), the scar type was found to be most common. A total of eight patients (5.7%) developed local recurrence, of which five were of nodular type and statistically significant ( $p=0.000$ ).

**Conclusion:** The most common type of ulcer healing was scar type after ESD, but nodular type was associated with local recurrence. When we perform follow-up endoscopy after ESD, we should pay attention to the lesion that has nodular change of mucosal surface.

**Keywords:** Early gastric cancer, endoscopic resection, recurrence after endoscopic resection

## INTRODUCTION

Early gastric cancer (EGC) is defined as a mucosal or submucosal lesion, without local lymph node metastasis, and can be treated by endoscopic resection (ER) (1-3). ER is widely performed as a standard treatment for EGC and can be divided into endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). ER is less invasive than surgical resection and has the advantage of providing a better quality of life for the patient (3). However, ER sometimes fails to completely remove the lesion (4). Although ESD achieves significantly higher en bloc resection and curative resection rates, local recurrence has been found after ESD as well (range: 1-5%) (5-7). In many studies, EMR is associated with a more higher local recurrence rate than ESD (range 2%-35%), because it is sometimes performed with a piecemeal resection (3,7). Therefore, patients with EGC who have undergone curative ER are routinely required to undergo scheduled sur-

veillance endoscopies to detect a local recurrence lesion or metachronous lesion.

Several studies have shown that piecemeal resection, positive of resection margin, large sized lesion (>3 cm), and location of lesion were significantly associated with local recurrence (6-9). To date, there are few reports on the clinical association between healing pattern of lesion and local recurrence after ER. Therefore, we examined the risk factors associated with local recurrence after ESD and the correlation between healing type of lesion and recurrence.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed the medical records of 293 patients who underwent ER of EGC or gastric adeno-

Presented in: *The abstract has been published on XXXI<sup>st</sup> International Workshop on Helicobacter & Microbiota in Inflammation & Cancer, September 14-15, 2018, Kaunas, Lithuania.*

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Received: September 27, 2018 Accepted: April 24, 2019

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DOI: 10.5152/tjg.2020.18764

ma at Dong-A University Hospital between April 2010 and January 2012. We analyzed the relationship among age, lesion location, size, pathologic diagnosis, presence of *Helicobacter pylori* (*H. pylori*), and healing types of ulcers in patients with local recurrence through follow-up endoscopic surveillance (1, 6, and 12 months after ESD). The criteria for excluding patients were as follows: patients who did not receive follow-up endoscopy at 1 month and 6 months after ER or tested for *H. pylori* and patients whose endoscopic image at the healing pattern of lesion was ambiguous. Finally, we analyzed 141 patients who underwent ER and clinicopathological features and clinical outcomes were obtained from a retrospectively collected database. The definition of indications for ER included the absolute criteria. The term 'absolute indications' is defined as an EGC which is a differentiated type of adenocarcinoma limited to the mucosa, a polypoid lesion  $\leq 2$  cm in size, and an excavated type  $\leq 1$  cm in size without concurrent ulceration (10).

#### ER procedures

All ESD procedures were performed by a single experienced endoscopist (J.S. Jang). ER was performed by either EMR or ESD. The patients were given (0.05 mg/kg) and pethidine (25 mg or 50 mg) intravenously prior to the ER. ER was performed by one experienced endoscopist using a standard single channel endoscope (EG-2990i; Pentax Corporation, Hoya Corporation, Tokyo, Japan). In the case of ESD, the lesion was confirmed and the marking point was placed outside the lesion by argon plasma clotting (Erbe Elektromedizin, Tübingen, Germany). After marking, submucosal solutions were injected into the submucosal layer by using a needle to lift the lesion. A circumferential incision was made into

the mucosa, and the submucosal layer was dissected using an IT knife (MTW Endoskopie Co. Ltd., Wesel, Germany). When bleeding or exposed vessels were observed, an endoscopic hemostasis was performed using hemostatic forceps (FD-410LR; Olympus) or hemoclips.

#### Follow-up schedule and *H. pylori* status

The patients underwent ER of EGC or adenoma and then were followed-up with endoscopy by forceps biopsy at 1 and 6 months. When ER specimen was judged to be non-curative resection such as positive vertical or lateral margin of EGC, SM cancer  $>500 \mu\text{m}$  from the muscularis mucosa, and positive vascular or lymphatic invasion on the pathologic reports, the patients received the additional surgical treatment.

The status of *H. pylori* infection was assessed by a rapid urease test (CLO; Kimberly-Clark, Roswell, GA) and a histologic test ((hematoxylin and eosin, Giemsa). *H. pylori* infection status was determined as positive if one or two of these tests were positive.

#### Healing type of gastric ulceration

After ER, the type of gastric ulcer healing was classified into three types on follow-up endoscopy (hypertrophic polypoid type, scar type, and nodular type). All of the follow-up endoscopy and classification of type were performed by a single experienced endoscopist (J.S. Jang). We defined the hypertrophic polypoid type at resection ulcer as reddish mucosal change and hyperthrophic change. The second is scar type. It is almost a grossly white, flat wound type. The third one is a nodular type, which is a case of grossly reddish or white nodularity change (Figure 1).

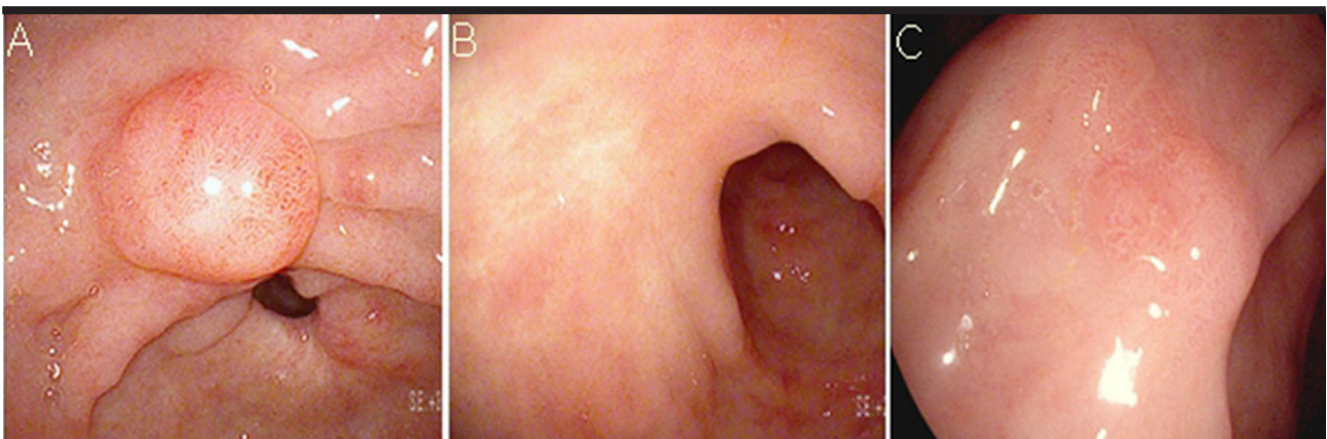


Figure 1. a-c. Healing type of gastric ulceration. (a) Hypertrophic polypoid type. (b) Scar type. (c) Nodular type.

**Statistical analysis**

Categorical variables were demonstrated as numbers with percentage and analyzed by chi-squared or Fisher’s exact test. Continuous variables were presented as means±standard deviation and analyzed by the Student t-test. A p-value of <0.05 was considered significant. All statistical analyses in this report were performed with Statistical Package for Social Sciences version 19.0 (SPSS Inc.; Chicago, IL, USA).

**RESULTS**

**Baseline characteristics**

The baseline clinicopathological characteristics are shown in Table 1. The mean age was 62.1 (±9.1) years, and 64.5% of the patients were male. Of these patients, 38 had well-differentiated adenocarcinoma, 16 had moderately differentiated adenocarcinoma, 26 had high-grade dysplasia, and 61 had low-grade dysplasia. The number of patients per location of lesion was 114 (80.9%) in the

lower third, 14 (9.9%) in the middle third, and 13 (9.2%) in the upper third. The patients were categorized according to the lesion size as 0-10 mm (16) (11.3%), 11-20 mm (76) (53.9%), 21-30 mm (40) (28.4%), and more than 30 mm (9) (6.4%); in addition, 47 (33.3%) were *H. pylori* positive and 94 (66.7%) were negative.

**The relationship between healing type of gastric ulceration and recurrence**

When the healing type of the ulcer was divided into hypertrophic polypoid type (9 cases (6.4%)), scar type (122 cases (86.5%)), and nodular type (10 cases (7.1%)), the scar type was found to be most common (Table 2). Among the 141 patients followed-up on with endoscopic surveillance, an event of local recurrence occurred in eight (5.7%) patients. There was a statistically significant recurrence in one (11.1%) of the hypertrophic polypoid type, two (1.6%) of the scar type, and five (50%) of the nodular type (Figure 2, Table 3).

The relationship between healing type of gastric lesion and factors

**Patient’s characteristics**

In hypertrophic polypoid type, all nine cases (100%) were male. There were 77 (63.1%) male and 45 (37.9%) female in the case of scar type and 5 (50%) male and 5 (50%) female in the case of nodular type (p=0.051). The mean age was 64.1±10.1 in the hypertrophic polypoid type, 61.7±9.2 in the scar type, and 64.7±8.0 in the nodular type (p=0.481, Table 4).

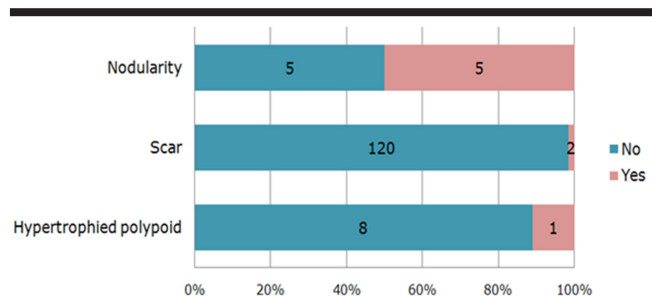
**Table 1.** Baseline clinical characteristics.

Characteristics	Value
Age, (year, mean±SD)	62.1±9.1
Male, no. (%)	91 (64.5)
Longitudinal location, no. (%)	
Upper one-third	13 (9.2)
Mid one-third	14 (9.9)
Lower one-third	114 (80.9)
Size, no. (%)	
0-10 mm	16 (11.3)
11-20 mm	76 (53.9)
21-30 mm	40 (28.4)
>30 mm	9 (6.4)
Pathological diagnosis, no. (%)	
Low-grade dysplasia	61 (43.3)
High-grade dysplasia	26 (18.4)
EGC, well differentiated	38 (27.0)
EGC, moderately differentiated	16 (11.3)
Helicobacter pylori infection (+), no. (%)	47 (33.3)

EGC: early gastric cancer; SD: standard deviation.

**Table 2.** Classification of healing pattern.

Healing pattern	No. (%)
Hypertrophic polypoid	9 (6.4%)
Scar	122 (86.5)
Nodular	10 (7.1)



**Figure 2.** Recurrence ratio of healing pattern after ESD. There was a statistically significant recurrence in the nodular type (p=0.000).

**Table 3.** Local recurrence rate and healing pattern.

	Hypertrophic polypoid	Scar	Nodular	p
Local recurrence				
No	8	120	5	
Yes	1	2	5	0.000

**Tumor characteristics**

The size of the lesion was 0-10 mm in two patients (22.2%), 11-20 mm in five patients (55.5%), 21-30 mm in two patients (22.2%), and more than 30 mm in 0 patients (0%) hypertrophic polypoid type. In the scar type, the size of the lesion was 0-10 mm (11) (9.0%), 11-20 mm (68) (55.7%), 21-30 mm (34) (27.8%), and more than 30 mm (9) (7.3%). In addition, in the nodular types, the size of

the lesion was 0-10 mm in three patients (30%), 11-20 mm in three patients (30%), 21-30 mm in four patients (40%), and 30 mm in 0 patients (0%). There was no significant correlation between tumor size and healing type ( $p=0.250$ , Table 4).

The lesion was located in the lower third of all patients in the hypertrophic polypoid type. The scar type was locat-

**Table 4.** Associated factor with healing pattern.

Characteristics	Hypertrophic polypoid	Scar	Nodular	p
Age, (years, mean±SD)	64.1±10.1	61.7±9.2	64.7±8.0	0.481
Sex, no				0.051
Male	9	77	5	
Female	0	45	5	
Tumor size, no.				0.250
0-10 mm	2	11	3	
11-20 mm	5	68	3	
21-30 mm	2	34	4	
>30 mm	0	9	0	
Longitudinal location, no.				0.531
Upper one-third	0	12	1	
Mid one-third	0	14	0	
Lower one-third	9	96	9	
Pathological diagnosis, no.				0.799
Low-grade dysplasia	4	54	3	
High-grade dysplasia	2	21	3	
EGC	3	47	4	

EGC: early gastric cancer; SD: standard deviation.

**Table 5.** Other associated factors with healing pattern.

Characteristics	Hypertrophic polypoid	Scar	Nodular	p
Helicobacter pylori infection, no.				0.577
Positive	4	41	2	
Negative	5	81	8	
Atrophy, no.				0.285
Mild	8	107	8	
Moderate	0	10	1	
Severe	0	3	1	
None	1	2	0	
Intestinal metaplasia, no.				0.878
Mild	7	93	8	
Moderate	1	13	0	
Severe	0	3	0	
None	1	13	2	

ed in the lower third (78.6%), in the middle third (14.4%), and in the upper third (12.8%). Nodular type was found in 90% (9 patients) in the lower third. There was no statistically significant correlation between the location of the lesion and the type of ulcer healing ( $p=0.531$ , Table 4).

In relation to pathological diagnosis and healing type, four cases (43.3%) of low-grade dysplasia, two cases (22.2%) of high-grade dysplasia, and three cases (33.3%) of adenocarcinoma were in the hypertrophic polypoid type. The scar type was low-grade dysplasia in 54 (44.2%), high-grade dysplasia in 21 (17.2%), and adenocarcinoma in 47 (38.5%) patients. In the nodular type, three patients (30%) had low-grade dysplasia, three patients had high-grade dysplasia (30%), and four patients (40%) had adenocarcinoma. Pathologic diagnosis of the tumor was not correlated with the type of ulcer healing ( $p=0.799$ , Table 4).

#### **H. pylori status**

In the hypertrophic polypoid type, *H. pylori* was positive in four (44.4%) and negative in five (55.5%) patients. In the scar type, 41 were *H. pylori* positive (33.6%) and 81 were *H. pylori* negative (66.4%). *H. pylori* was positive in two (20%) and negative in eight (80%) patients in the nodular type. *H. pylori* status was not significantly correlated with the type of ulcer healing ( $p=0.577$ , Table 5).

#### **Atrophic change**

The hypertrophic polypoid group had eight cases (88.9%) with mild atrophic change and one case (11.1%) without atrophic change. In the scar type, there were 107 cases (87.7%) with mild atrophic change, 10 cases (8.2%) with moderate atrophic change, 3 cases (2.5%) with severe atrophic change, and 2 cases (1.6%) without atrophic change. There were eight cases (80%) with mild atrophic change and two cases (20%) without atrophic change in the nodular type. The presence of atrophic changes was not significantly correlated with the healing type ( $p=0.285$ , Table 5).

#### **Intestinal metaplasia**

The hypertrophic polypoid group had seven cases (77.8%) with mild intestinal metaplasia (IM), one case (11.1%) with moderate IM, and one case (11.1%) without IM. In the scar type, there were 93 cases (76.2%) with mild IM, 13 cases (10.7%) with moderate IM, 3 cases (2.5%) with severe IM, and 13 cases (10.7%) without IM. The nodular type had eight cases (80%) with mild IM and two cases (20%) without mild IM. The presence of IM was not significantly correlated with the healing type ( $p=0.878$ , Table 5).

#### **DISCUSSION**

Although radical gastrectomy with regional lymphadenectomy is the mainstay of curative treatment for EGC (11), ER is less invasive than surgical resection and improves quality of life and plays a major role in EGC treatment (3). However, because ER preserves most of the stomach, the risk of local and metachronous recurrence in patients after ER for EGC is a major concern during follow-up of these patients (12,13). In many previous studies, the incidence of synchronous or metachronous tumor after post-ESD was relatively higher than that after gastrectomy (9,12,14,15). Therefore, follow-up endoscopic surveillance plays an important role for detecting recurrent lesions in the remnant stomach after ESD. However, there are no universally accepted guidelines for the optimal monitoring endoscopic interval or the time of follow-up endoscopy needed after curative ESD. Although follow-up with abdominal ultrasonography or CT scan as well as annual or biannual endoscopy after ER for EGC is recommended in the Japanese gastric cancer treatment guidelines (16), follow-up CT scans can have a low benefit in detecting early recurrences, because most recurrence cases are mucosal lesions or low incidence of lymph node metastasis (6,17-19). Therefore, we examined the risk factor associated with local recurrence after ESD and the correlation between healing type of lesion and recurrence when undergoing scheduled follow-up endoscopies.

An endoscopic exam is an effective way to detect recurrence of EGC. Several studies have shown that incomplete resection is the most significantly associated one with local recurrence (6,7,19,20). Another study showed that tumor size and location are independent risk factors for local recurrence after ER (7). In the present study, recurrence was observed in 8 of 141 patients (5.7%). The majority of local recurrence at the scar were in the nodular type in five patients (50%) and showed a significant correlation ( $p=0.000$ ). Another study about ER scar showed that follow-up biopsy may not be needed when there is a flat mucosa without hyperemic changes in the scar (21). However, this study divided the resection scar into too many groups (three morphology types, two mucosal defect types, presence of hyperemic change, and spontaneous bleeding) and the extended indications were also included. In contrast, our study only targeted patients with absolute indications, and it is easy to apply during follow-up endoscopy because of only three categories.

There are some limitations to our study. First, this study was a single-center retrospective study and the number of patients was relatively small due to many cases of follow-up loss. In the patients of recurrence, there were a few patients with presence of *H. pylori*, and most of the

patients had mild status of atrophic change, IM. Despite these limitations, this study showed that during surveillance endoscopy after ESD, we should pay attention to the lesion that has nodular change of mucosal surface. In addition, we included EGC and gastric adenoma in the study group. Although there is a difference between the biologic features of gastric cancer and adenoma, other studies have reported the incidence of gastric cancer after ER for gastric adenoma was not significantly different from that of EGC (22). In this regard, not only EGC patients but also gastric adenoma patients were included in the study group.

In summary, regular follow-up endoscopic monitoring can reduce the recurrence. In addition, we need to be careful when follow-up endoscopy indicates a nodular change at the scar.

**Ethics Committee Approval:** Ethics committee approval for this study was received from the Ethics Committee of Dong-A University.

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

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - J.S.C.; Design - J.S.C.; Supervision - J.S.J.; Resources - J.S.J.; Materials - J.H.C.; Data Collection and/or Processing - J.H.C.; Analysis and/or Interpretation - J.H.C.; Literature Search - J.H.C.; Writing Manuscript - J.H.C.; Critical Review - J.S.C.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received financial support by Dong-A university fund-2018.

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