

ORIGINAL ARTICLE

Prognostic analysis of gastric mucosal dysplasia after endoscopic resection: A single-center retrospective study

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Summary

Purpose: To analyze the prognostic factors of gastric mucosal dysplasia after endoscopic resection.

Methods: 362 patients with gastric mucosal dysplasia diagnosed by endoscopic biopsy and undergoing endoscopic resection from March 2012 to March 2016 were enrolled. Follow-up was longer than 30 months. Basic characteristics of enrolled patients were recorded, including age, gender, surgical procedures, lesion location, pathological type, lesion size, *Helicobacter pylori* (HP) infection, operation time and wound area. The relationship between the above factors and postoperative residual lesions and recurrence after endoscopic resection of gastric mucosal dysplasia was analyzed.

Results: Included were 200 males and 162 females, aged 28-78 years, (mean 59.3±11.5). Operation time and wound area were not correlated with postoperative recurrence of gastric mucosal dysplasia resected by endoscopic mucosal resection (EMR) ($p>0.05$). Operation time in patients undergoing endoscopic submucosal dissection (ESD) was longer compared with those of controls ($p=0.032$). Additionally, wound area

was smaller in patients with postoperative residual disease ($p=0.003$) and postoperative recurrence ($p=0.048$) after ESD compared with controls. Intestinal metaplasia was a common risk factor for postoperative residual disease and postoperative recurrence of gastric mucosal dysplasia. Lesion location and complete resection were independent risk factors for postoperative recurrence of gastric mucosal dysplasia. Also, pathological findings and HP infection were independent risk factors for recurrence of gastric mucosal dysplasia after endoscopic resection.

Conclusions: In patients undergoing ESD of gastric mucosal dysplasia, prolonged operation time may increase the possibility of postoperative residual disease. Complete resection may reduce the possibility for recurrence. Intestinal metaplasia may serve as a common independent risk factor for postoperative residual disease and recurrence of gastric mucosal dysplasia after endoscopic resection.

Key words: dysplasia, endoscopy, postoperative recurrence, postoperative residual disease, risk factors

Introduction

Carcinogenesis of gastric mucosa is a long-term and complicated process. Currently, the pathogenesis of gastric cancer (GC) is triggered from chronic atrophic gastritis, intestinal metaplasia and dysplasia. Gastric mucosal dysplasia is a precancerous lesion and closely related to the occurrence of GC. In 2000, the concept of gastric intraepithelial neoplasia (GIN) has been proposed

[1]. GIN is classified into low grade intraepithelial neoplasia (LGIN) and high grade intraepithelial neoplasia (HGIN) according to the degree of cell dysplasia and structural disorder. Early gastric cancer (EGC) refers to the presence of gastric cancer lesions in the mucosa or submucosa, regardless of the lesion size and lymph node metastasis. According to the guidelines for GC treatment in Japan,

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HGIN belongs to EGC and can be accompanied by invasive adenocarcinoma. About 25% of HGIN patients will progress to adenocarcinoma within 1 year [2,3].

In recent years, with the application of endoscopic diagnostic techniques such as CLE (confocal laser endomicroscopy) and magnifying endoscopy, the detection rate of EGC has risen. Particularly, endoscopic mucosal dissection (EMD) and endoscopic submucosal dissection (ESD) have been widely applied instead of traditional surgical resection due to their advantages of small trauma, good safety, high efficacy and good compliance. EMR and ESD have become the preferred options for patients with gastric precancerous lesions and EGC. However, some GC patients may experience postoperative residual lesions or recurrence after EMR and ESD. A series of studies have found that the residual disease rate of GC is 2.7-14% after endoscopic treatment [4-8], and the recurrence rate ranges from 1.2-19.2% [8-10]. This study retrospectively analyzed 362 patients with gastric mucosal dysplasia who underwent endoscopic treatment with an aim to explore the prognostic factors of gastric mucosal dysplasia after endoscopic resection.

Methods

Patients

362 patients with gastric mucosal dysplasia diagnosed by endoscopic biopsy undergoing endoscopic treatment from March 2012 to March 2016 were enrolled. Endoscopic treatments included ESD and EMR. Follow-up lasted longer than 30 months. The clinical data of the 362 enrolled patients were retrospectively analyzed. Included were 200 males and 162 females, aged 28-78 years (mean 59.3±11.5). Exclusion criteria were: younger than 18 years old; pregnant and lactating women; with severe liver and kidney dysfunction; allergic to sputum. This study was approved by the Ethics Committee of the Wuxi No.9 Hospital Affiliated to Soochow University, and the enrolled patients signed informed consent before the study entry.

Clinical data

Collected were medical records, endoscopy examination reports, treatment records, and histological examination reports of enrolled patients. Basic characteristics of each patient were recorded, including age, gender, surgical procedures, lesion location, pathological type, lesion size, HP infection, operation time and wound area. Patients were followed up for longer than 30 months. The follow-up endoscopy was performed at 1 month, 3 months, and 6 months after surgery. If the main endoscopic manifestations were mucosal bulge, roughness and depression without obvious gastric mucosal abnormality, patients were due for endoscopy examination a year later. Otherwise, patients were required for biopsy,

and a specific treatment plan would be developed based on the pathological results.

Definition of residual lesions or recurrence

Gastric mucosal dysplasia was pathologically confirmed based on the new Vienna classification of epithelial neoplasia of the gastrointestinal tract [11]. The postoperative disease course was characterized as postoperative residual lesions and recurrence. In this study, residual disease was defined as biopsy-proven presence of dysplasia at the surgery site within 12 months after endoscopic resection. Recurrence was defined as presence of dysplasia at the surgery site after 12 months. Patients were assigned into control group, residual group and recurrence group. All cases were pathologically confirmed independently by three pathologists with over 30-year working experience.

Statistics

SPSS 19.0 statistical software (IBM, Armonk, NY, USA) was used for statistical analyses. The quantitative data were compared with Student's t-test. Univariate and multivariate Cox regression analyses for postoperative residual and recurrence were used. P<0.05 indicated statistically significant difference.

Table 1. Basic characteristics of enrolled patients

Characteristics	n (%)
Sex	
Male	200 (55.2)
Female	162 (44.8)
Age, years	
≥65	179 (49.4)
<65	183 (50.6)
Dysplasia	
Low grade	264 (72.9)
High grade	98 (27.1)
En bloc resection	
Yes	297 (82.0)
No	65 (18.0)
Location	
Cardia & fundus ventriculi	69 (19.1)
Corpora ventriculi	123 (34.0)
Sinuses ventriculi	170 (46.9)
Size (cm)	
≥3	97 (26.8)
<3	265 (73.2)
Resection method	
ESD	161 (19.8)
EMR	201 (80.2)
HP infection	
Yes	271 (74.9)
No	91 (25.1)
Intestinal metaplasia	
Yes	140 (38.7)
No	222 (61.3)

For abbreviations see text

Results

Basic characteristics of enrolled patients

Basic characteristics of enrolled patients are listed in Table 1. The enrolled patients included 200 males and 162 females, aged 28-78 years (mean 59.3±11.5). LGIN cases accounted for 72.9% of all enrolled patients, and 38.7% of resected lesions were pathologically confirmed as intestinal metaplasia. A total of 297 (82%) patients underwent complete resection and most of them received EMR (80.2%). Lesions were mainly distributed in the gastric antrum (46.9%) and the majority (70.5%) were smaller than 3 cm in diameter.

Surgical procedures analyses

In this study, there were 201 and 161 patients undergoing ESD and EMR, respectively (Table 1). Operation time and wound area were analyzed as surgical procedure related factors. Operation

time and wound area were not correlated to postoperative recurrence of gastric mucosal dysplasia resected by EMR ($p>0.05$). However, longer operation time was found in patients undergoing ESD compared with those of controls ($p=0.032$). Additionally, wound area was smaller in patients with postoperative residual disease ($p=0.003$) and postoperative recurrence ($p=0.048$) who underwent ESD than those of controls (Figure 1).

Analysis of risk factors affecting postoperative residual lesions and postoperative recurrence

Postoperative residual lesions were correlated with resection method, lesion location, lesion size and intestinal metaplasia ($p<0.05$, Table 2). In particular, the residual rate of patients with lesions >3 cm was significantly higher than those with lesions <3 cm ($p<0.001$). Long-term postoperative recurrence was associated with age, pathology, HP infection and intestinal metaplasia ($p<0.05$, Table 3).

Table 2. The relationship between control group and residual group

	Control group	Residual group	<i>p</i>
Sex			0.091
Male	110	41	
Female	105	24	
Age, years			0.463
≥ 65	98	33	
<65	117	32	
Dysplasia			0.439
Low grade	162	52	
High grade	53	13	
<i>En bloc</i> resection			0.010
Yes	185	47	
No	30	18	
Location			0.031
Cardia & fundus ventriculi	42	13	
Corpora ventriculi	76	19	
Sinuses ventriculi	97	33	
Size(cm)			0.000
≥ 3	44	29	
<3	171	36	
Resection method			0.831
ESD	96	30	
EMR	119	35	
HP infection			0.053
Yes	159	40	
No	56	25	
Intestinal metaplasia			0.000
Yes	59	33	
No	156	32	

For abbreviations see text

Risk factors with statistical significance were analyzed by Cox regression analysis. Intestinal metaplasia was the common independent risk factor for postoperative residual lesions and recurrence of gastric mucosal dysplasia after endoscopic resection. Lesion location and complete resection were positive independent risk factors for postoperative recurrence of gastric mucosal dysplasia. Besides, pathological findings and HP infection were positive independent risk factors for recurrence of gastric mucosal dysplasia after endoscopic resection (Table 4).

Discussion

Gastric mucosal lesions manifest as erosion, depression or uplift of the gastric mucosa. Clear pathological diagnosis of HGIN in routine biopsy is always needed. According to the guideline proposed in 2010, GIN is characterised as clear epithe-

lial neoplastic hyperplasia with cellular and structural atypia, but no evidence of invasive growth [12]. In our study enrolled patients were diagnosed as HGIN or early adenocarcinoma by routine endoscopy and biopsy. No invasion of the muscularis propria and lymph node metastasis were observed. The lesion size and growth pattern under the microscopy were not taken into consideration. The 10-year survival of HGC patients without lymph node metastasis who underwent EMR for complete resection was up to 99% [13]. However, gastric mucosal lesions larger than 20 mm are difficult to be completely resected at one time. Accurate pathological evaluation of the fragmented lesions is difficult, leading to a higher recurrence than those of complete resection [4,14,15].

Influencing factors of recurrence of gastric mucosal dysplasia after endoscopic resection have not been fully studied. It is reported that a variety of causes may be involved in, including age

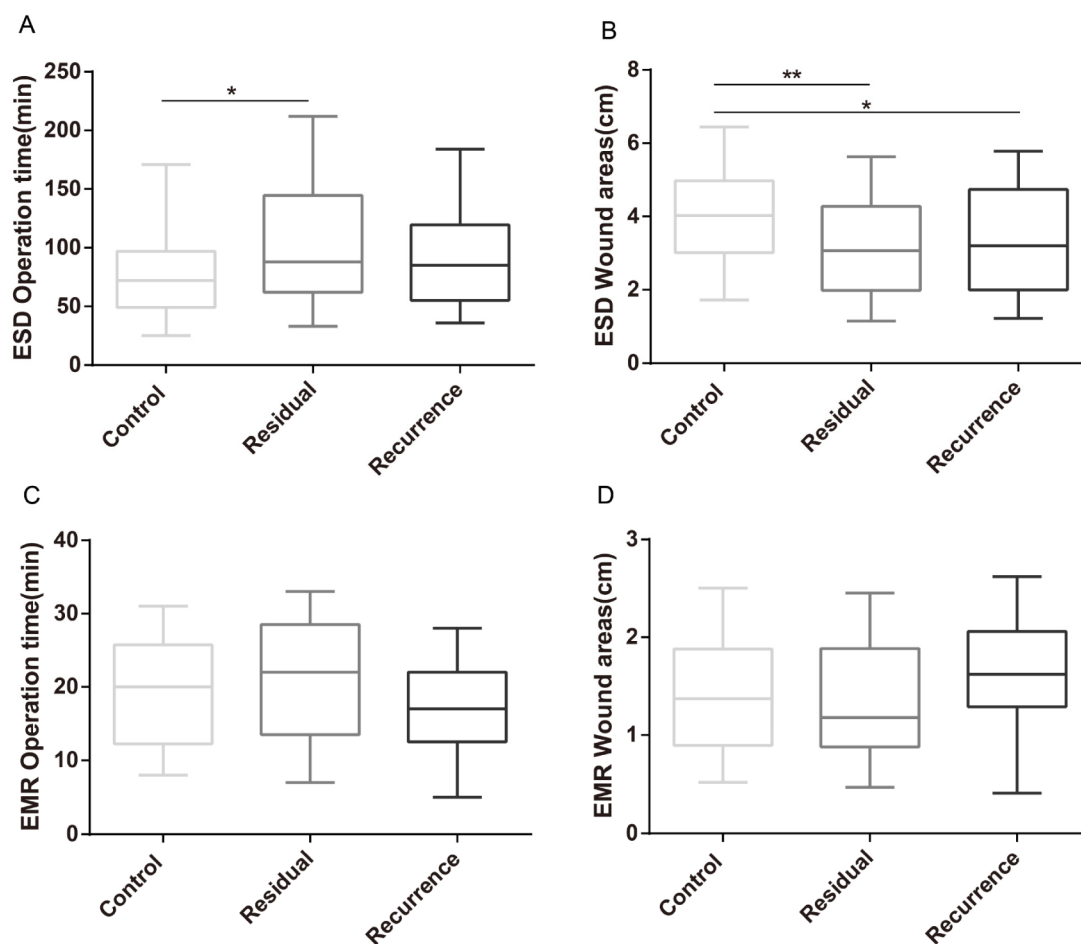


Figure 1. Relationship between surgical procedures and prognosis of gastric mucosal dysplasia after endoscopic resection. **(A):** Operation time in patients undergoing ESD was longer compared with those of controls ($p=0.032$). **(B):** Wound area was smaller in patients with postoperative residual disease ($p=0.003$) and postoperative recurrence ($p=0.048$) who underwent ESD than those of controls. **(C):** Operation time was not correlated to postoperative recurrence of gastric mucosal dysplasia resected by EMR ($p>0.05$). **(D):** Wound area was not correlated to postoperative recurrence of gastric mucosal dysplasia resected by EMR ($*p<0.05$, $**p<0.01$).

[6,10,16], gastric mucosal atrophy [10], undifferentiated histology [17], upper gastric surgery [17] and HP infection [18-21]. This study explored the factors influencing postoperative residual lesions and postoperative recurrence of HGC.

Complete resection is one of the factors affecting postoperative recurrence of GC. In the en-

doscopic resection, *en bloc* resection refers to the complete resection of the lesion at one time. The procedures in which lesion needs to be resected for multiple times is called piecemeal resection [22]. ESD exerts advantages of wider resection range and higher rate of *en bloc* resection compared with EMR. According to the lesion margin and basal

Table 3. The relationship between control group and recurrence group

	Control group	Recurrence group	p
Sex			0.184
Male	110	49	
Female	105	33	
Age, years			0.046
≥65	98	48	
<65	117	34	
Dysplasia			0.014
Low grade	162	50	
High grade	53	32	
<i>En bloc</i> resection			0.152
Yes	185	65	
No	30	17	
Location			0.536
Cardia & fundus ventriculi	42	14	
Corpora ventriculi	76	28	
Sinuses ventriculi	97	40	
Size (cm)			0.106
≥3	44	24	
<3	171	58	
Resection method			0.760
ESD	96	35	
EMR	119	47	
HP infection			0.010
Yes	159	72	
No	56	10	
Intestinal metaplasia			0.000
Yes	59	48	
No	156	34	

For abbreviations see text

Table 4. Multivariate analysis of clinical factors associated with postoperative residual disease and recurrence

	Residual group			Recurrence group		
	OR	95% CI	p	OR	95% CI	p
Age	-	-	-	1.631	0.847-3.143	0.144
Dysplasia	-	-	-	1.737	0.992-3.040	0.053
<i>En bloc</i> resection	1.641	1.114-2.416	0.011	-	-	-
Location	2.513	1.222-5.167	0.012	-	-	-
Size	0.728	0.478-1.108	0.139	-	-	-
HP infection	-	-	-	1.871	1.048-3.343	0.034
Intestinal metaplasia	3.247	1.555-6.776	0.002	2.885	1.745-4.768	<0.001

tumor tissue infiltration, the endoscopic surgical margin can be divided into complete resection, incomplete resection and unable to evaluate [23]. Gotoda et al. [12] reviewed the complete resection rate of EGC by ESD which was 79-100%, and the recurrence rate was 0-1% in Japan. This study considered that incomplete resection is a risk factor affecting postoperative residual lesions.

Our study specifically emphasized the relationship between postoperative residual disease and postoperative recurrence. According to the results, the factors affecting postoperative residual disease and postoperative recurrence were not exactly the same. In this study, intestinal metaplasia was the common independent risk factor for postoperative residual disease and recurrence of gastric mucosal dysplasia after endoscopic resection. Besides, lesion location and incomplete resection were independent risk factors for endoscopic resection of gastric mucosal dysplasia. Pathological findings and HP infection were independent risk factors for recurrence after endoscopic resection of gastric mucosal dysplasia. It is considered that the resection of cardioplastic dysplasia at the junction of the esophagus and stomach is difficult to be operated, which increases the residual disease rate. Previous studies [18-21] have already reported that HP infection could increase the postoperative recurrence rate of CG, which was consistent with our study.

In addition, this study investigated the relationship between surgical procedures and postop-

erative recurrence in different resection methods. The results showed that prolonged operation time of endoscopic procedures may increase the possible rate of postoperative residual lesions. We believed that the prolonged operation time is caused by the rich blood supply and the complex shape of the lesion. Wound area was related to postoperative residual lesions and postoperative recurrence, suggesting that appropriate expansion of the surgical margin can help to reduce recurrence of GC.

Some limitations in this study still need to be specially considered. Since it is a retrospective analysis with a small sample size, further studies should expand the sample size to further explore the way to improve prognosis after endoscopic resection of gastric mucosal dysplasia.

Conclusions

During endoscopic resection of gastric mucosal dysplasia, prolonged operation time may increase the possibility of postoperative residual disease. Expansion of gastric mucosal resection margin may reduce the possibility for recurrence. Intestinal metaplasia may serve as a common independent risk factor for postoperative residual disease and recurrence of gastric mucosal dysplasia after endoscopic resection.

Conflict of interests

The authors declare no conflict of interests.

References

1. Gotoda T, Yanagisawa A, Sasako M et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219-25.
2. Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007;10:1-11.
3. Evans JA, Chandrasekhara V, Chathadi KV et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. *Gastrointest Endosc* 2015;82:1-8.
4. Kim JJ, Lee JH, Jung HY et al. EMR for early gastric cancer in Korea: a multicenter retrospective study. *Gastrointest Endosc* 2007;66:693-700.
5. Nasu J, Doi T, Endo H, Nishina T, Hirasaki S, Hyodo I. Characteristics of metachronous multiple early gastric cancers after endoscopic mucosal resection. *Endoscopy* 2005;37:990-3.
6. Yang XW, Zhu SH, Li PZ, Li WZ, Sun XL. Outcomes of laparoscopic gastrectomy for gastric cancer in elderly patients. *JBUON* 2018;23:85-91.
7. Nakajima T, Oda I, Gotoda T et al. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? *Gastric Cancer* 2006;9:93-8.
8. Kato M, Nishida T, Yamamoto K et al. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. *Gut* 2013;62:1425-32.
9. Kobayashi M, Narisawa R, Sato Y, Takeuchi M, Aoyagi Y. Self-limiting risk of metachronous gastric cancers after endoscopic resection. *Dig Endosc* 2010;22:169-73.
10. Han JS, Jang JS, Choi SR et al. A study of metachronous cancer after endoscopic resection of early gastric cancer. *Scand J Gastroenterol* 2011;46:1099-1104.

11. Stolte M. The new Vienna classification of epithelial neoplasia of the gastrointestinal tract: advantages and disadvantages. *Virchows Arch* 2003;442:99-106.
12. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006;41:929-42.
13. Pech O, Gossner L, May A, Vieth M, Stolte M, Ell C. Endoscopic resection of superficial esophageal squamous-cell carcinomas: Western experience. *Am J Gastroenterol* 2004;99:1226-32.
14. Uedo N, Iishi H, Tatsuta M et al. Longterm outcomes after endoscopic mucosal resection for early gastric cancer. *Gastric Cancer* 2006;9:88-92.
15. Muto M, Miyamoto S, Hosokawa A et al. Endoscopic mucosal resection in the stomach using the insulated-tip needle-knife. *Endoscopy* 2005;37:178-82.
16. Jang MY, Cho JW, Oh WG et al. Clinicopathological characteristics of synchronous and metachronous gastric neoplasms after endoscopic submucosal dissection. *Korean J Intern Med* 2013;28:687-93.
17. Seo JH, Park JC, Kim YJ, Shin SK, Lee YC, Lee SK. Undifferentiated histology after endoscopic resection may predict synchronous and metachronous occurrence of early gastric cancer. *Digestion* 2010;81:35-42.
18. Lim JH, Kim SG, Choi J, Im JP, Kim JS, Jung HC. Risk factors for synchronous or metachronous tumor development after endoscopic resection of gastric neoplasms. *Gastric Cancer* 2015;18:817-23.
19. Bae SE, Jung HY, Kang J et al. Effect of *Helicobacter pylori* eradication on metachronous recurrence after endoscopic resection of gastric neoplasm. *Am J Gastroenterol* 2014;109:60-7.
20. Kim YI, Choi IJ, Kook MC et al. The association between *Helicobacter pylori* status and incidence of metachronous gastric cancer after endoscopic resection of early gastric cancer. *Helicobacter* 2014;19:194-201.
21. Bang CS, Baik GH, Shin IS et al. *Helicobacter pylori* Eradication for Prevention of Metachronous Recurrence after Endoscopic Resection of Early Gastric Cancer. *J Korean Med Sci* 2015;30:749-6.
22. Takeuchi T, Ota K, Harada S et al. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol* 2013;13:136.
23. Rosch T, Sarbia M, Schumacher B et al. Attempted endoscopic en bloc resection of mucosal and submucosal tumors using insulated-tip knives: a pilot series. *Endoscopy* 2004;36:788-801.