

Clinical Impact of Second-Look Endoscopy after Endoscopic Submucosal Dissection of Gastric Neoplasms

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Background/Aims: One major complication of endoscopic submucosal dissection (ESD) is delayed bleeding. Most hospitals routinely perform second-look endoscopy to reduce the chances of delayed bleeding without solid evidence supporting the practice. The aim of this study was to evaluate whether second-look endoscopy prevents delayed bleeding and to verify the clinicopathological features of delayed bleeding to determine how to identify lesions that may require second-look endoscopy. **Methods:** We investigated 440 lesions in 397 patients who underwent ESD for gastric neoplasm from January 2008 to June 2010. Two-thirds of the enrolled cases were adenomas, and 290 lesions were located in the lower portion of the stomach. Clinically evident bleeding from mucosal defects 24 hours after ESD was considered as delayed bleeding. We reviewed the data, including the characteristics of patients, lesions, and procedures. Furthermore, the rate of delayed bleeding before and after second-look endoscopy, performed within three days of ESD, was investigated to determine the utility of second-look endoscopy. **Results:** Delayed bleeding was evident in 9 of 440 lesions (2.0%), all of which underwent endoscopic hemostasis. The only significant factor predicting delayed bleeding was resected specimen over 40 mm in size ($p=0.003$). Delayed bleeding occurred in 8 of 9 cases (89%) before the second-look endoscopy, which was performed within 72 hours after ESD. **Conclusions:** In this study, second-look endoscopy may be useful for preventing post-ESD bleeding, especially when resected specimens are over 40 mm in size. (*Gut Liver* 2012;6:316-320)

Key Words: Hemorrhage; Endoscopic hemostasis; Stomach neoplasms; Endoscopic resection

INTRODUCTION

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are accepted treatments for gastric adenomas (GA) and early gastric cancer (EGC). ESD is often preferred, as it has a better success rate for en bloc resections than EMR.^{1,2} One concern about ESD is that it creates artificial ulcers, and delayed bleeding has been reported in about 5% of patients.³ In most cases, endoscopic hemostasis effectively stops bleeding during an emergency endoscopy. Therefore, it is necessary to determine the nature of delayed bleeding and appropriate management. Several studies have found that tumor location (i.e., middle or lower third of the stomach),^{4,5} tumor size,⁶⁻⁸ and ulcerative findings⁷ are independent risk factors for delayed bleeding. Most hospitals routinely perform second-look endoscopy to check for delayed bleeding, though there is little solid evidence to support this practice. One report suggested that second-look endoscopy after gastric ESD contributes little to preventing delayed bleeding.³ However, this result contradicted our experience. Therefore, we evaluated whether second-look endoscopy prevents delayed bleeding and verified the clinicopathological features of delayed bleeding to identify specific lesions that may need second-look endoscopy.

MATERIALS AND METHODS

1. Patients and materials

A total of 450 lesions with a histologic diagnosis of gastric epithelial neoplasias consecutively treated with ESD at Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea from January 2008 to June 2010 were retrospectively reviewed. ESD was principally indicated for adenomas and possible node negative EGCs according to the criteria of Gotoda *et al.*⁹ based on endoscopic findings including

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Received on July 26, 2011. Revised on October 9, 2011. Accepted on November 2, 2011. Published online on May 2, 2012.

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl.2012.6.3.316>

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chromoendoscopy with biopsy and endoscopic ultrasonographic findings. Adenomas were defined as lesions diagnosed as mucosal neoplasia of category 3 and 4.1 according to the revised Vienna classification. All operators were experts, each of whom had performed ESD over 100 times for more than 3 years. Eight lesions were excluded from the study because perforation caused by their specific physiological conditions occurred during ESD, and 2 lesions were excluded due to bleeding within 24 hours after ESD, leaving 148 EGCs and 292 GAs (Fig. 1). The Ethical Committee of the Kosin University College of Medicine approved the study.

2. ESD procedures

The ESD protocol was as follows.^{10,11} All patients provided written informed consent before treatment. Patients fasted the morning of the procedure, which was performed under conscious sedation. Marks were made 5 mm outside the tumor edge with an argon plasma coagulator (PSD-60; Olympus, Tokyo, Japan). Epinephrine (1:100,000 solution in saline) was injected into the submucosal layer around the lesion, and the mucosa were cut at the marks. After cutting the mucosa, the lesion was dissected using an insulation tipped diathermic knife (KD-610L; Olympus) or flex knife (KD-630L; Olympus), and all visible vessels on the ulcer floor were coagulated with a hot biopsy forcep (FD-1L-1; Olympus). When the saline and epinephrine mixture (1:100,000) alone did not sufficiently elevate the tumor, hyaluronic acid was used. After removing lesions from the stomach, we routinely treated nonbleeding visible vessels and oozing as the final step of ESD.

3. Second-look and urgent endoscopies

Principally, second-look endoscopy was performed mainly on postoperative day (POD) 2, but also was performed on POD 1 or POD 3 due to holidays after ESD. The purpose of second-look endoscopy was to check for recent hemorrhage or possible bleeding (nonbleeding visible vessels) on the mucosal defect. When bleeding or nonbleeding visible vessels were seen on second-look endoscopy, prophylactic hemostasis was performed. Clipping was performed with hemostatic clips (HX-610-135; Olympus) for large nonbleeding vessels, and thermocoagulation with a hot biopsy forcep was performed for bleeding vessels, small nonbleeding vessels, or in locations that were difficult to clip due to tissue consolidation. Argon plasma coagulator was used to ablate oozing and surrounding tissue or small visible vessels. In cases of clinically evident bleeding after ESD, the patient underwent urgent endoscopy with endoscopic hemostasis on bleeding spots or nonbleeding visible vessels, mainly by clipping or thermocoagulation. Blood transfusion was performed for patients with hematochezia, hematemesis, or hypotension. Just after ESD, pantoprazole 40 mg per day was administered intravenously and continuously. After POD 3, one of the following proton pump inhibitors was administered orally: 20 mg rabeprazole, 40 mg omeprazole, or 30 mg lansoprazole once daily, these were considered equally effective for acid suppression.¹² Most patients resumed food intake from POD 2 just after second-look endoscopy and discharged at POD 6 unless there was bleeding. Patients were also asked to contact their physicians in case of hematemesis or melena after discharge. When

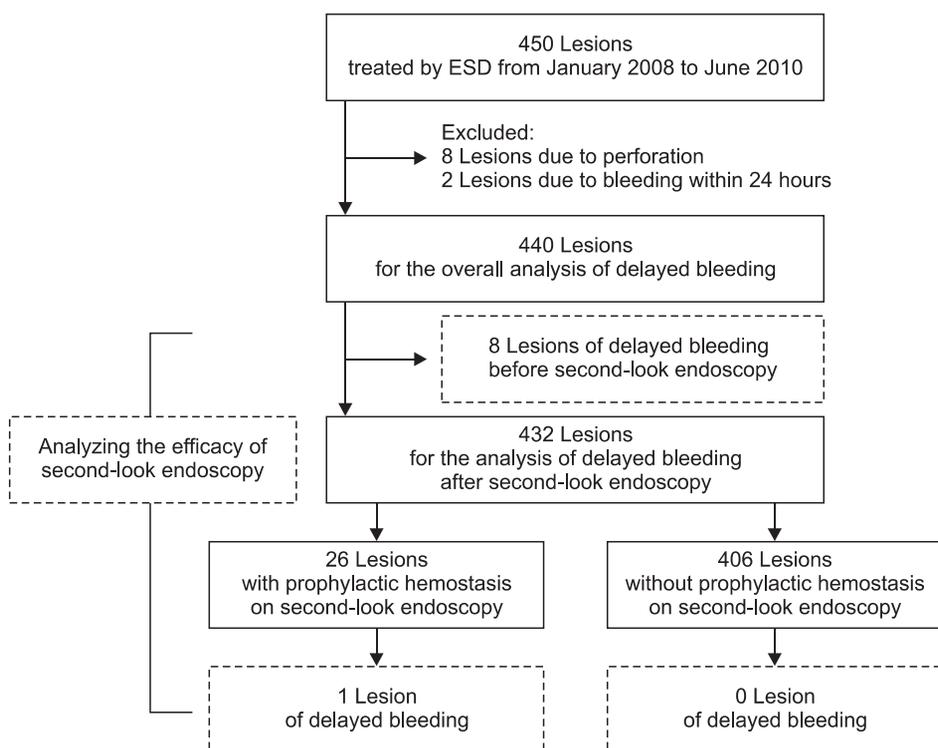


Fig. 1. Flowchart for analyzing the efficacy of second-look endoscopy to prevent delayed bleeding. ESD, endoscopic submucosal dissection.

perforation or delayed bleeding occurred, the discharge schedules including food intake were changed according to patient condition. The total follow-up duration was 60 days when almost all artificial ulcers were considered to be cured.¹³

4. Data analysis

Delayed bleeding was defined as clinically evident bleeding, including melena, hematochezia, and hematemesis, with detectable evidence of bleeding from mucosal defect by urgent endoscopy 24 hours after ESD. Urgent endoscopy was defined as emergent endoscopy to control massive bleeding from the mucosal defect after ESD in the presence of hematemesis, hematochezia or melena. The following variables were analyzed to investigate factors influencing delayed bleeding: age, sex, comorbidities (hypertension, diabetes mellitus, heart disease, chronic renal failure, and liver cirrhosis), and the use of anticoagulants and/or antiplatelet drugs (patient-related factors); the location (upper third, middle third, or lower third of the stomach), circumference (anterior wall, posterior wall, lesser curvature, or greater curvature), gross EGC type, tumor size (maximum and minimum diameter of the resected tumor), resected specimen size (maximum and minimum diameter of the resected specimen), and histologic type (EGC differentiation); the ESD period; and bleeding pattern on emergency endoscopy (spurting, oozing, exposed vessel, spot, or clots) and transfusion for postoperative bleeding. The rates of delayed bleeding before and after second-look endoscopy were investigated to determine the utility of second-look endoscopy. A flow chart for analyzing the efficacy of second-look endoscopy is shown in Fig. 1.

5. Statistical analysis

Statistical analysis was performed using the SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Student's t-test was performed for age, tumor size, specimen size, and ESD period. χ^2 test were used for probability for sex, comorbidities, anticoagulant and/or antiplatelet drug use, location, circumference, gross type, and histologic differentiation. If there was more than one predictor with a significant difference by univariate analysis, multivariate analysis using a logistic regression model was planned. The analysis of delayed bleeding was performed using the Kaplan-Meier method. Difference in the frequency of delayed bleeding before and after second-look endoscopy was accessed. Statistical significance was set at a p-value of <0.05.

RESULTS

Delayed bleeding occurred in 9 (2.0%) of 440 lesions and were successfully managed with endoscopic treatment; no surgical intervention was required. No delayed bleedings were followed by rebleeding. In 88% of delayed bleeding, 8 of 9, blood transfusions were performed. The univariate analysis of variables predicting delayed bleeding is shown in Table 1. Re-

Table 1. Characteristics of Patients with Delayed Bleeding after ESD

Characteristic	Delayed bleeding (n=9)	Nonbleeding (n=431)	p-value
Age, yr	66.3±9.8	63.8±9.2	0.408
Sex, male/female	8/1	306/125	0.457
Size of specimen, mm	42.1±11.2	30.2±9.8	<0.001
Size of lesion, mm	22.3±10.3	18.9±8.5	0.070
Specimens over 40 mm	6 (66.7)	84 (18.7)	0.003*
Duration of procedure, min	63.0±40.1	47.6±77.3	0.552
Anticoagulants/Platelets [†]	0 (0.0)	23 (5.3)	1.000
Location of lesion			
Longitudinal			
Upper	1 (11.1)	23 (5.3)	0.684
Middle	3 (30.3)	123 (28.5)	
Lower	5 (55.6)	285 (66.2)	
Circumferential			
AW	2 (22.2)	96 (22.3)	0.939
PW	2 (22.2)	108 (25.5)	
LC	1 (11.1)	26 (6.0)	
GC	4 (44.5)	201 (45.2)	
Differentiation of cancer group			0.679
Well	3 (50.0)	55 (38.7)	
Moderate	3 (50.0)	87 (61.2)	
Type of lesion			0.489
Elevated	5 (55.6)	290 (67.3)	
Flat	0 (0.0)	20 (4.6)	
Depressed	4 (44.4)	121 (89.1)	
Underlying disease			0.696
Angina	0 (0.0)	13 (3.0)	
CVA	0 (0.0)	2 (0.4)	
DM	0 (0.0)	49 (11.4)	
HTN	2 (22.2)	88 (20.4)	

Data are presented as mean±SD or number (%). All data were analyzed by Fisher's exact test except age, specimen size, lesion size, and procedure duration, which were analyzed using a Student's t-test. ESD, endoscopic submucosal dissection; Upper, upper third; Middle, middle third; Lower, lower third; AW, anterior wall; PW, posterior wall; LC, lesser curvature; GC, greater curvature; Angina, angina pectoris; CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension.

*When the resected specimen was greater than 4 cm, the positive predictive value of delayed bleeding was 66.5%; [†]The administration of anticoagulant, aspirin, warfarin, plavix, or clopidogrel medication was 7 days prior to ESD.

sected specimen size was the only difference between delayed bleeding and non-bleeding groups (42.1±11.1 mm vs 30.2±9.8 mm, p<0.001). A resected specimen over 40 mm was considered a single predictor of delayed bleeding (p=0.003; odd ratio [OR], 8.26; 95% confidence interval [CI], 2.025 to 33.714). The positive predictive value for delayed bleeding with a resected

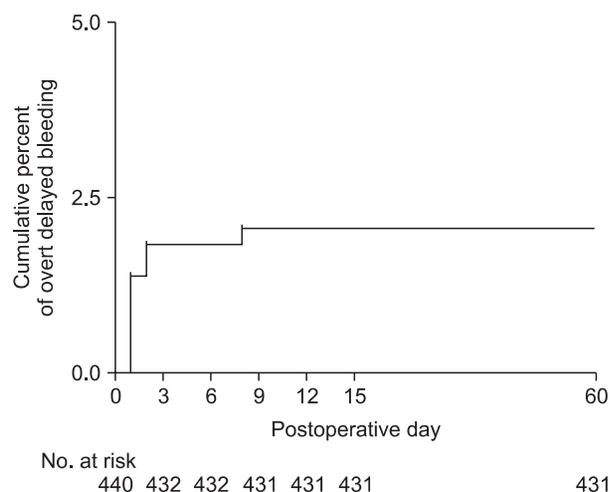


Fig. 2. The frequency of delayed bleeding is significantly reduced after second-look endoscopy, which was principally performed by postoperative day 2 (8 cases [89%] vs 1 case [11%]).

specimen over 40 mm was 66.5%. Multivariate analysis was not performed because univariate analysis identified only one predictor.

The median duration between ESD and second look endoscopy was 2 days (range, 1 to 3), and was performed most frequently on POD 2 (95% of second look endoscopies). Delayed bleeding controlled by urgent endoscopy was divided into 4 categories: spurting (2 cases), oozing (4 cases), exposed vessel (1 case), and old blood clots (1 case). Delayed bleeding occurred much less frequently after second-look endoscopy (8 cases [89%] vs 1 case [11%]) (Fig. 2). One of the 26 lesions with prophylactic hemostasis and none of the 406 without prophylactic hemostasis showed delayed bleeding after second-look endoscopy; the only case of delayed bleeding after second-look endoscopy was observed on POD 8. In this case, the resected specimen was 54 mm in size and was located on the anterior wall side of the distal antrum.

DISCUSSION

A previous retrospective study suggested that second-look endoscopy to prevent delayed bleeding might be excessive or unnecessary.³ According to Goto *et al.*,³ the frequencies of delayed bleedings between before second-look endoscopy and after second-look endoscopy were not significantly different. In our study, however, more delayed bleedings occurred before second-look endoscopy than after (8 cases [89%] vs 1 case [11%]).

Treating nonbleeding visible vessels at the end of ESD reduced delayed bleeding significantly, although it could not prevent it completely.⁵ After controlling nonbleeding visible vessels, newly developing visible vessels on the ulcer bed may contribute to bleeding in some cases, which may be detected by second-look endoscopy. Although second-look endoscopy did

not prevent all delayed bleeding in our series, the present study showed that treating potential bleeding foci and the surrounding tissue in second-look endoscopy decrease delayed bleeding after second-look endoscopy. However, these findings do not prove that second-look endoscopy is beneficial but suggest that it is too early to say that second-look endoscopy after gastric ESD contributes little to preventing delayed bleeding without randomized controlled trials. The reason why late bleeding cases are few may not be the effect of second-look endoscopy but merely the process of natural healing.

According to several studies, tumor location,^{4,5} tumor size,^{6,8} and ulcerative findings⁷ were independent predictive factors for delayed bleeding. When the resected specimen is over 40 mm, the risk of delayed bleeding increases 8.2 fold, which agrees with the results of a previous study.¹⁴ Furthermore, the chance of delayed bleeding is 66.5%. These findings suggest that endoscopists should carefully treat possible bleeding foci and may need to perform second-look endoscopy when removing specimens over 40 mm in size. Moreover, facing the fact that especially in patients with a resected specimen with a diameter of more than 40 mm, most bleeding episodes occurred within 48 hours, it is carefully recommended to perform second-look endoscopy on POD 1 in these high risk patients.

Our study has two substantial limitations. First of all, about two-thirds of enrolled cases are adenomas, 292 out of 440 cases, so large number of adenomas lead relatively many cases of lesions at lower portion of the stomach. In our study, the lesions at upper or middle portion were apparently fewer than the other articles. Goto *et al.*³ suggested that postoperative bleeding tends to occur early in cases in the lower portion and late in cases in the upper portion. If we had more cases in the upper portion, late bleeding cases after second-look endoscopy might have increased. Second, the predictive factor in our study was not a lesion size but a specimen size. If ESD was precisely performed, a specimen size should be determined by a lesion size. However, practically, specimen sizes were not regularly proportional to a lesion size. This might be the reason why specimen size, not lesion size, was the only predictive factor for delayed bleeding.

In conclusion, based on our retrospective analysis with slightly off-centered data toward lesions in the lower third of the stomach or GA, second-look endoscopy may have value for preventing delayed bleeding, especially when the resected specimen is over 40 mm in size. A randomized controlled trial will be desirable to elucidate the efficacy of second-look endoscopy after ESD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Kosin University College of Medicine (2011).

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