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The role of second-look endoscopy in endoscopic submucosal dissection for early gastric cancer

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Background/aims: *Delayed bleeding is a major complication of endoscopic submucosal dissection. Second-look endoscopy is routinely performed in most hospitals to reduce the possibility of delayed bleeding without solid evidence to support this practice. The aim of this study was to evaluate whether second-look endoscopy prevents delayed bleeding, and to verify clinicopathological features of delayed bleeding in order to identify lesions that may benefit from a second-look endoscopy.* ***Materials and Methods:*** *We investigated 392 lesions in 388 patients who underwent endoscopic submucosal dissection for early gastric cancer from January 2006 to July 2011. Clinically evident bleeding from mucosal defects 24 hours after endoscopic submucosal dissection was considered delayed bleeding. Data including characteristics of patients, lesions, and procedures were reviewed. Furthermore, the rate of delayed bleeding before and after second-look endoscopy, performed within three days of endoscopic submucosal dissection, was investigated to determine the utility of second-look endoscopy.* ***Results:*** *Delayed bleeding was evident in 12 of 392 lesions (3,1%), all of which achieved endoscopic hemostasis. The only significant factor predicting delayed bleeding was a resected specimen size of over 40 mm (OR=6,200, 95% CI=1,912 – 20,108). Delayed bleeding occurred more frequently prior to the second-look endoscopy (p=0,022).* ***Conclusions:*** *In our endoscopic submucosal dissection data about early gastric cancer, it is too early to conclude that second-look endoscopy is not a valuable procedure, and second-look endoscopy may be useful for preventing post-endoscopic submucosal dissection bleeding, especially in resected specimens greater than 40 mm in size.*

Key words: Hemorrhage, endoscopic hemostasis, gastric cancer, endoscopic resection

İkinci bakış endoskopisinin erken mide kanserinin endoskopik submukozal diseksiyonunda rolü

Giriş ve Amaç: *Endoskopik submukozal diseksiyonun majör bir komplikasyonu gecikmiş kanamadır. Yapılması yönünde geçerli kanıtlar olmasa da birçok hastanede gecikmiş kanama ihtimalini azaltmak amacıyla ikinci bakış endoskopisi yapılmaktadır. Bu çalışmanın amacı, gecikmiş kanamanın önlenmesinde ikinci bakış endoskopisinin rolünü araştırmak ve bu kanamaların klinikopatolojik rolünü değerlendirerek hangi lezyonların gecikmiş kanamaya neden olduğunu tanımlamaktır.* ***Gereç ve Yöntem:*** *Ocak 2006'dan Temmuz 2011'e kadar 388 hastada erken gastrik kanser için endoskopik submukozal diseksiyon yapılan 392 lezyon araştırıldı. Endoskopik submukozal diseksiyondan 24 saat sonra, mukozal defektlerden olan klinik olarak bariz kanamalar gecikmiş kanama olarak değerlendirildi. Hastaların, lezyonların ve prosedürlerin özellikleri gözden geçirildi. Ayrıca, ikinci bakış endoskopisinin rolünü belirlemek amacıyla, bundan önce ve 3 gün sonra yapılan endoskopi ile de sonraki gecikmiş kanamalar araştırıldı.* ***Bulgular:*** *Gecikmiş kanama, 392 lezyonun 12'sinde (%3,1) gerçekleşti ve hepsinde de endoskopik hemostaz sağlandı. Gecikmiş kanamayı öngören tek risk faktörü rezeke edilen spesimenin 40 mm'den büyük olmasıdır (OR=6,200, 95% CI=1,912-20,108). Gecikmiş kanama çoğunlukla ikinci bakış endoskopisinden önce olmuştur (p=0,022).* ***Sonuç:*** *Erken gastrik kanser için endoskopik submukozal diseksiyon yapılan vakalarda ikinci bakış endoskopisinin yararı olmadığını söylemek için erken olmakla birlikte, özellikle rezeke edilen spesimenin 40 mm'den büyük olduğu durumlarda ikinci bakış endoskopisi gecikmiş kanamayı önlemek için yararlı olabilir.*

Anahtar kelimeler: Kanama, endoskopik hemostaz, gastrik kanser, endoskopik rezeksiyon

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INTRODUCTION

Endoscopic mucosal resection (EMR) has been widely applied for mucosal tumors of the gastrointestinal (GI) tract. Conventionally, the indications for EMR included mucosal lesions of the intestinal type no larger than 2 cm for protruded lesions, and no larger than 1 cm for depressed lesions without ulcer findings. However, since 2000, endoscopic submucosal dissection (ESD) has been applied to much larger lesions, resulting in larger artificial ulcers. The validity of ESD for large mucosal tumors has been discussed from the points of lymph node metastasis and technical problems for en-bloc resection (1-3). However, it is essential to consider the safety of this procedure on the healing process of large artificial ulcers in the postoperative period.

One major concern about ESD is that it creates artificial ulcers, and delayed bleeding has been reported in about 5% of patients (4). Most hospitals routinely perform a second-look endoscopy to check for delayed bleeding, though there is little solid evidence to support this practice. Two reports have suggested that a second-look endoscopy after gastric ESD does not contribute significantly in the prevention of delayed bleeding (4, 5). However, this has been held true in our experience. Therefore, we aimed to determine whether second-look endoscopy is helpful in preventing delayed bleeding. Additionally, we analyzed the clinicopathological features of delayed bleeding to identify specific lesions that are prone to delayed bleeding.

MATERIALS and METHODS

Patients and materials

A total of 405 lesions with a histologic diagnosis of early gastric cancer (EGC) treated with ESD at our institution from January 2006 to June 2011 were retrospectively reviewed. ESD was principally indicated for possible node-negative EGCs according to the criteria established by Gotoda et al. based on chromoendoscopy with biopsy, endoscopic ultrasonographic findings and adenomas (1). All operators were experts, and had performed atleast 100 ESDs for a period of greater than three years. Nine lesions were excluded due to perforation caused by patient-specific physiological conditions that occurred during ESD, and 4 lesions were excluded due to bleeding within 24 hours after ESD, leaving 392 EGCs (Figure 1). The study was approved by the Ethical Committee of the Kosin University College of Medicine.

ESD procedures

The ESD protocol was as follows (6, 7). Informed consent was obtained from all patients prior to treatment. Patients were required to fast the morning of the operation, which was performed under conscious sedation. An area of 5 mm outside the tumor edge was marked 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 was incised at the marks. After incising the mucosa, the lesion was dissected using an insulation tipped diathermic knife (KD-610L, Olympus, Tokyo, Japan) or Flex knife (KD-630L; Olympus, Tokyo, Japan), and all visible vessels on the ulcer floor were coagulated using hot biopsy forceps (FD-1L-1, Olympus, Tokyo, Japan). When the saline and epinephrine mixture (1:100.000) alone did not sufficiently elevate the tumor, hyaluronic acid was used. After all gastric lesions were removed, non-bleeding visible vessels and oozing were routinely treated as the final step of ESD.

Second-look and urgent endoscopies

The second-look endoscopy was performed mainly on post-operative day (POD) 2, but also was performed on POD 1 or POD 3 due to scheduling reasons. The purpose of the second-look endoscopy was to assess for recent hemorrhage or possible bleeding (non-bleeding visible vessels) at the mucosal defect. When bleeding or non-bleeding visible vessels were seen on second-look endoscopy, prophylactic hemostasis was performed. Clipping was performed with hemostatic clips (HX-610-135, Olympus, Tokyo, Japan) for large non-bleeding vessels, and thermocoagulation with hot biopsy forceps was performed for bleeding vessels, small non-bleeding vessels, or in locations that were difficult to clip due to tissue consolidation. The argon plasma coagulator was used to ablate oozing, small visible vessels or any surrounding tissue. In cases of clinically evident bleeding after ESD, an urgent endoscopy with endoscopic hemostasis on bleeding areas or non-bleeding visible vessels was performed, mainly by clipping or thermocoagulation. Blood transfusions were given to patients with hematochezia, hematemensis, or hypotension. Post-procedure, 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

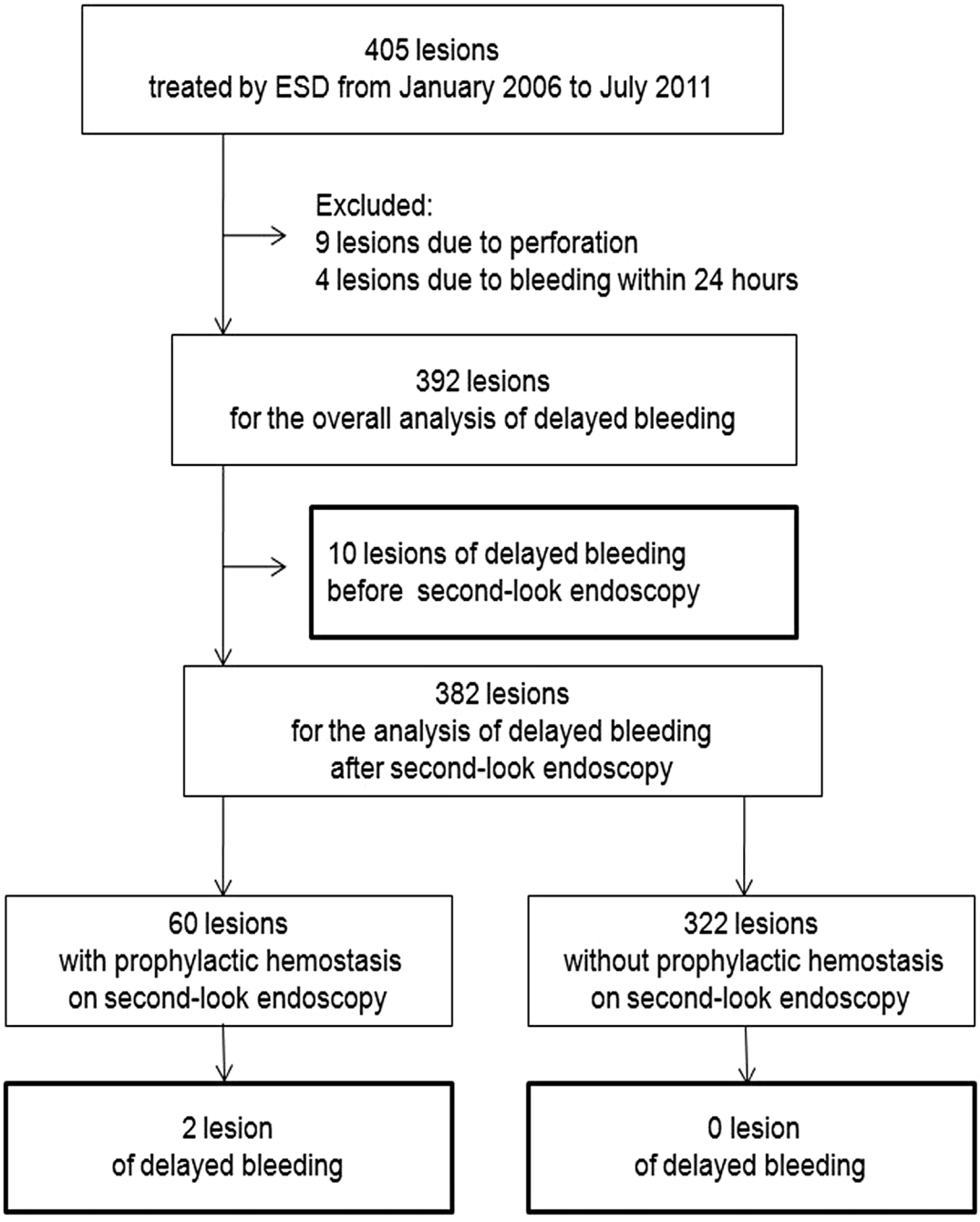


Figure 1. Flowchart for analyzing the efficacy of second-look endoscopy to prevent delayed bleeding. ESD: endoscopic submucosal dissection.

acid suppression (8). Most patients resumed food intake on POD 2 just after second-look endoscopy and discharged home on POD 6 unless there was evidence of bleeding. Patients were instruct to contact their physicians in case of hematemesis or melena after discharge. When perforation or delayed bleeding occurred, the discharge schedules including food intake were changed depending on the patient's condition. The total follow-up duration was 60 days when almost all artificial ulcers were considered to have been cured (9).

Data analysis

Delayed bleeding was defined as clinically evident bleeding including melena, hematochezia, and hematemesis, with detectable evidence of bleeding from the mucosal defect on urgent endoscopy performed 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, co-morbidities (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 analyzing the efficacy of second-look endoscopy is shown in Figure 1.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 16.0, SPSS, Chicago, IL, USA). Student's t-test was performed for age, tumor size, specimen size, and ESD period. Chi-square testing was performed to evaluate probabilities for sex, comorbidities, anticoagulant and/or antiplatelet drug use, location, circumference, gross type, and histologic differentiation. If more than one predictor with a significant difference was noted on univariate analysis, multivariate analysis using a logistic regression model was planned. An analysis of delayed bleeding was performed using the Kaplan-Meier method. Differences in the frequency of delayed bleeding before and after second-look endoscopy were studied. Statistical significance was set at a p-value of < 0.05.

RESULTS

Frequency of delayed bleeding

Delayed bleeding occurred in 12 (3,0%) of 392 lesions and was successfully managed with endoscopic treatment; no surgical intervention was required. No case of delayed bleeding experienced further rebleeding. Eight patients (66,7%) with delayed bleeding required blood transfusions. The median duration between ESD and second-look endoscopy was 2 days (range 1-3), and was performed most frequently on POD 2 (95% of second-look endoscopies). Delayed bleeding occurred less frequently after second-look endoscopy (p=0,022; Figure 2). Two of 60 lesions were treated with prophylactic hemostasis, and none of the 302 cases without prophylactic hemostasis showed evidence of delayed bleeding after second-look endoscopy.

Risk factor for delayed bleeding

Univariate analysis of variables predicting delayed bleeding is shown in Table 1. Resected specimen size was the only difference noted in patients with delayed bleeding when compared with the non-bleeding groups (43,0±10,1 mm vs. 32,1±9,7 mm, p<0,001). A resected specimen size greater than 40 mm was considered a single predictor of delayed bleeding (p=0.001, odds ratio=6,200, and 95% confidence interval=1,912–20,108). The positive predictive value for delayed bleeding with a resected specimen over 40 mm was 63,8%. Multivariate analysis was not performed because univariate analysis identified only one predictor.

DISCUSSION

Two retrospective studies have suggested that second-look endoscopy to prevent delayed bleeding might be excessive or unnecessary (4, 5). The frequencies of delayed bleeding between before and

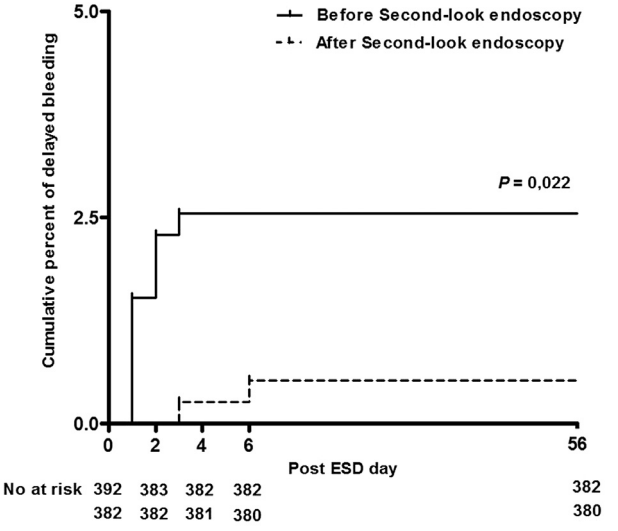


Figure 2. The frequency of delayed bleeding is significantly reduced after second-look endoscopy principally performed by postoperative day 2 ($P = 0,022$, Hazard Ratio = 3,763, and 95% Confidence interval = 1,211 – 11,700).

Table 1. Characteristics of delayed bleeding and control groups after ESD

		Delayed bleeding (n = 12)	Non-bleeding (n = 380)	P value
Age (mean±SD, year)		65,3±10,8	63,2±9,1	0,411
Sex (male/female)		9/3	299/81	0,725
Size of specimen (mean±SD, mm)		43,0±10,1	32,1±9,7	< 0,001
Size of lesion (mean±SD, mm)		25,6±12,3	19,9±10,9	0,068
Specimens over 40 mm, n (%)		6 (66,7)	88 (23,1)	0,001*
Duration of procedure (mean±SD, min)		66,1±45,2	49,6±81,7	0,572
Anticoagulants/platelets†, n (%)		1 (2,0)	50 (13,1)	> 0,999
Location of lesion, n (%)				
Longitudinal	Upper	3 (25,0)	79 (20,7)	0,878
	Middle	5 (41,7)	148 (38,9)	
	Lower	4 (33,3)	153 (40,4)	
Circumferential	AW	2 (16,7)	88 (23,2)	0,945
	PW	3 (25,0)	101 (26,6)	
	LC	3 (25,0)	80 (21,0)	
	GC	4 (33,3)	111 (29,2)	
Resection style, n (%)				0,034
	En bloc	10 (91,7)	372 (97,9)	
	Piecemeal	2 (8,3)	8 (2,2)	
Tumor depth, n (%)				> 0,999
	Mucosa	12 (100)	374 (98,4)	
	Submucosa	0 (0,0)	6 (1,6)	
Type of lesion, n (%)				0,056
	Elevated	5 (41,7)	271 (67,3)	
	Flat	2 (16,6)	20 (4,6)	
	Depressed	5 (41,7)	89 (89,1)	
Underlying disease, n (%)				
	Angina	0 (0,0)	25 (6,6)	> 0,999
	CVA	1 (8,3)	5 (1,3)	0,171
	DM	1 (8,3)	33 (8,7)	> 0,999
	HTN	2 (16,7)	87 (22,9)	> 0,999

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. All data were analyzed by Fisher's exact test except for age, specimen size, lesion size, and duration of procedure: analyzed by Student's t-test.

*When the resected specimen is over 4 cm, the positive predictive value of delayed bleeding is 63,8%.

†All anticoagulants, aspirin, warfarin, plavix, and clopidogrel, were held 7 days prior to ESD.

after second-look endoscopy were not significantly different (4, 5). In our study, however, more delayed bleedings occurred before second-look endoscopy than after (p=0,022).

Although treating non-bleeding visible vessels at the end of ESD did not prevent delayed bleeding completely, it seemed to reduce delayed bleeding significantly (10). After controlling non-bleeding 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. Second-look endoscopy did not prevent all delayed bleeding in our series, but the present study has shown that delayed bleeding decreased significantly after second-look endoscopy. However, while these findings do not prove that second-look endoscopy is beneficial, they suggest that it may be too early to conclude that second-look endoscopy after gastric ESD contributes little to preventing delayed bleeding, especially without randomized controlled trials. Of course, the reason for such few late bleeding cases may be natural healing, and notsecond-look endoscopy.

Several studies have suggested that tumor location (10, 11), tumor size (12-14), and ulcerative findings (13) are independent predictive factors for delayed bleeding. When the resected specimen is over 40 mm, the risk of delayed bleeding increases

6,2 fold, which is in agreement with the results from a previous study (15). Furthermore, the chance of delayed bleeding is 63.8%. Based on these findings, we suggest that endoscopists should carefully treat possible bleeding foci after ESD when removing specimens over 40 mm in size. Moreover, it is recommended that the observation period for patients with a ESD specimen size greater than 40 mm or over.

Our study has two substantial limitations. First, the predictive factor in our study was not lesion size, but specimen size. If ESD is precisely performed, specimen size should be determined by lesion size. However, practically, specimen sizes are not regularly proportional to lesion size. This might be the reason why specimen size, not lesion size, was the only predictive factor for delayed bleeding. Second, this is a retrospective study in a single center. Therefore, we cannot say that second-look endoscopy is effective for the prevention of delayed bleeding after ESD. We can only suggest that it is too early to conclusively state that second-look endoscopy is not effective.

In conclusion, based on our retrospective analysis, it is too early to judge that second-look endoscopy is not a valuable procedure. Additionally, second-look endoscopy may be useful for preventing post-ESD bleeding, especially when the resected specimen size is over 40 mm.

Declaration of interest: *The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.*

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