

Second-Look Endoscopy after Gastric Endoscopic Submucosal Dissection for Reducing Delayed Postoperative Bleeding

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Background/Aims: This study evaluated the role of a second-look endoscopy after gastric endoscopic submucosal dissection in patients without signs of bleeding. **Methods:** Between March 2011 and March 2012, 407 patients with gastric neoplasms who underwent endoscopic submucosal dissection for 445 lesions were retrospectively reviewed. After the patients had undergone endoscopic submucosal dissection, they were allocated to two groups (with or without second-look endoscopy) according to the following endoscopy. The postoperative bleeding risk of the lesions was not considered when allocating the patients. **Results:** The delayed postoperative bleeding rates did not differ between the two groups (with vs without second-look endoscopy, 3.0% vs 2.1%; $p=0.546$). However, a tumor in the upper-third of the stomach (odds ratio [OR], 5.353; 95% confidence interval [CI], 1.075 to 26.650) and specimen size greater than 40 mm (OR, 4.794; 95% CI, 1.307 to 17.588) were both independent risk factors for delayed postoperative bleeding. Additionally, second-look endoscopy was not related to reduced delayed postoperative bleeding. However, delayed postoperative bleeding in the patients who did not undergo a second-look endoscopy occurred significantly earlier than that in patients who underwent a second-look endoscopy (4.5 and 14.0 days, respectively, $p=0.022$). **Conclusions:** A routine second-look endoscopy after gastric endoscopic submucosal dissection is not necessary for all patients. (**Gut Liver 2015;9:43-51**)

Key Words: Second-look endoscopy; Endoscopic submucosal dissection; Bleeding; Delayed bleeding; Hemostasis

INTRODUCTION

Early gastric cancers (EGCs) that are confined to the mucosa and lack of lymph node metastasis can be cured by an endoscopic resection, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), rather than by gastrectomy.^{1,2} Compared with EMR, ESD methods can resect gastric lesions in a single piece regardless of tumor size.^{3,4} In addition, it is less invasive, less costly, and requires a shorter hospital stay than surgical resection.^{3,4} Accordingly, ESD is now widely accepted as the optimal endoscopic treatment method for early gastric neoplasms in Asian countries.^{1,4-6}

However, requires a great level of endoscopic skill, takes a lengthy procedure time, and occasionally results in major complications, such as perforation and significant bleeding,⁷⁻⁹ though the frequency of these complications has been decreasing with improvements to technique and instrumentation. Post-ESD bleeding is difficult to predict and can be a potentially life-threatening complication. Especially, delayed post-ESD bleeding which occurred after patients were discharged is a concern for both endoscopists and patients, because urgent treatment for bleeding, such as transfusion or emergency endoscopy, is difficult in outpatient setting. Unfortunately, effective prevention methods of delayed post-ESD bleeding have not yet been well established.

With regard to peptic ulcer bleeding, there have been several reports about the effectiveness of a second-look endoscopy after the initial endoscopic hemostasis.¹⁰⁻¹² Although the clinical usefulness of a second-look endoscopy is still controversial in cases of acute peptic ulcer bleeding, some randomized controlled studies suggest that a scheduled second endoscopy may reduce the recurrence of bleeding.^{11,12} However, the role of a routine post-ESD second-look endoscopy in cases with no signs

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of bleeding has not been fully characterized.^{13,14} Therefore, we conducted a study to evaluate whether performing a post-ESD second-look endoscopy before patients were discharged could reduce the risk of delayed post-ESD bleeding.

MATERIALS AND METHODS

1. Patient database

Clinical data from consecutive patients who underwent ESD for gastric adenoma and EGC were prospectively collected at Severance Hospital, Seoul, Korea from March 2011 to March 2012. These data included patient demographics, tumor characteristics, ESD results, implementation of second-look endoscopy and its findings, and post-ESD complications, including bleeding. The locations and macroscopic types of gastric neoplasm were classified according to the Japanese Gastric Cancer Association system.¹⁵ ESD was indicated for possible node-negative EGC according to the criteria of Gotoda *et al.*,^{4,16} which are as follow: (1) differentiated adenocarcinoma, intramucosal cancer, without ulcer findings, irrespective of the tumor size; (2) differentiated adenocarcinoma, intramucosal cancer, with ulcer findings, ≤30 mm in size; (3) differentiated adenocarcinoma, minute submucosal penetration (sm1; 500 μm penetration into submucosa), without ulcer findings, ≤30 mm in size; and (4) undifferentiated intramucosal cancer, without ulcer findings, ≤20 mm in size. All lesions were assessed by endoscopy with biopsy prior to ESD. In addition, patients with EGC underwent endoscopic ultrasonography in order to predict depth of invasion. In cases of gastric adenoma, ESD was performed when there was a chance of foci of malignancy or if the patients strongly desired the procedure.

Second-look endoscopies were performed within 3 days of ESD as the scheduled esophagogastroduodenoscopy. During the second-look endoscopy, the artificial ulcer was meticulously

examined. The bleeding site was treated with electrical coagulation when either spurting hemorrhage (Forrest Ia), oozing hemorrhage (Forrest Ib), or a visible vessel (Forrest IIa) was noted.¹⁷

A total of 481 consecutive lesions in 442 patients underwent ESD. Of these, 22 lesions with a post-ESD perforation were excluded from this study. Another 14 lesions which showed post-ESD bleeding before second-look endoscopy was performed were excluded. The remaining 445 lesions were enrolled in this study. After the patients had undergone ESD, they were allocated to two groups according to the following endoscopy: group with second-look endoscopy and the other group without second-look endoscopy. Postoperative bleeding risk of the lesions was not under consideration for allocating the patients. In addition, only endoscopists who had performed 300 cases or more of ESD were involved in this study. As a result, 140 patients with 165 lesions underwent a second-look endoscopy, and 267 patients with 280 lesions did not. Fig. 1 shows the flow chart of the patients included in this study. The Institutional Review Board of Severance Hospital approved this study.

2. ESD methods

Six attending gastroenterologists performed ESD in this study. All the procedures were performed under moderate sedation using intravenous propofol administered by anesthesiologists. Vital signs were continuously monitored during the procedure. The typical procedure sequence consisted of marking, mucosal incision, and submucosal dissection with simultaneous hemostasis. ESD was performed with a standard single-channel endoscope (GIF-H260Z; Olympus Optical Co., Ltd., Tokyo, Japan). After several marking dots were circumferentially placed outside the lesion using a needle knife (KD-10Q-1-A; Olympus Optical Co., Ltd.) or a needle-knife papillotome (MTW Endoskopie, Wesel, Germany), a saline solution containing epinephrine (0.01 mg/mL) mixed with indigo carmine was injected into

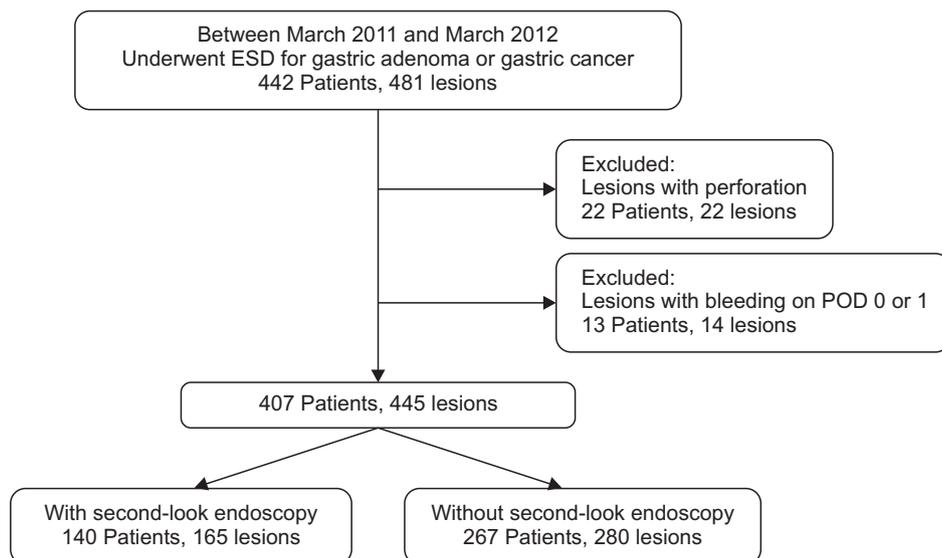


Fig. 1. Flow chart of the patients included in this study. ESD, endoscopic submucosal dissection; POD, postoperative day.

the submucosal layer using a 21-gauge needle to lift the lesion off the muscle layer. A circumferential incision was made in the mucosa using a needle knife and an insulated-tip (IT) knife (KD-610L; Olympus Optical Co., Ltd.). The submucosal layer was dissected directly with one of the following knives: IT knife, hook knife, flex knife, or dual knife, until complete removal was achieved. Endoscopic hemostasis was performed with a hemoclip or hemostatic forceps whenever bleeding or exposed vessels were observed.

Drugs that can cause a bleeding tendency such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin were discontinued 5 to 7 days before ESD. These drugs were restarted about 2 weeks after ESD if postoperative bleeding did not develop. Standard dose proton pump inhibitor (PPI) was administered to all patients for at least 4 weeks after ESD. PPI was administered intravenously for the first 3 days and orally thereafter. Soft diet was given on the following day from ESD. In addition, all patients received an education about diet and lifestyle before discharge.

3. Histologic evaluation and assessment of resection efficacy

All resected specimens were systematically sectioned at 2 mm intervals, centered on the part of the lesion closest to the margin and the site of the deepest invasion. Histological assessment was based on the Vienna classification.¹⁸ Final pathologic diagnoses were classified as low grade dysplasia, high grade dysplasia, differentiated EGC, or undifferentiated EGC.

4. Definitions and outcome measures

En bloc resection was defined as resection in a single piece as opposed to the resection of multiple pieces. The complete resection of *en bloc*-resected tumors was defined as lateral and vertical margins free of tumor on histologic examination. The complete resection of piecemeal-resected tumors was defined as the entire removal of the tumors and sufficient tumor-free margins after reconstruction of all pieces. Procedure time was defined as the time from marking to complete removal, including the time required for hemostasis. Bleeding was defined as the occurrence of clinical symptoms, such as melena or hematemesis. All suspected bleeding lesions were confirmed by performing emergent endoscopy. In addition, delayed post-ESD bleeding was defined as the bleeding which occurred at ESD site after 2 days from ESD. A diagnosis of perforation required the direct endoscopic observation of mesenteric fat or the presence of free air on an abdominal radiography or computed tomography scan.

5. Statistical analysis

Categorical variables including *en bloc* and complete resection rate, procedure time which was categorized, and post-ESD bleeding rate were analyzed using a chi-square test. Continuous variables, such as age, were analyzed with the t-test. Variables with significance 0.2 or less in univariate analysis and second-

look endoscopy performance were included in a logistic regression model. Age, which showed a difference in the baseline characteristics of patients, was also adjusted in logistic regression analysis. The date of post-ESD bleeding was compared using a Mann-Whitney U test. A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics

The baseline characteristics of the patients and lesions are shown in Table 1. The mean age of the patients with second-look endoscopy was younger than that of the patients without second-look endoscopy (with second-look endoscopy vs without, 62.7 ± 9.2 years vs 64.5 ± 8.7 years; $p = 0.047$). The percentage of male patients were 71.4% and 77.2% in the patients with and without second-look endoscopy, respectively. The percentage of patients with hypertension was higher in patients without second-look endoscopy than in patients with second-look endoscopy (with second-look endoscopy vs without, 37.1% vs 47.6%; $p = 0.044$). *Helicobacter pylori* infection was more frequent in patients with second-look endoscopy than in patients without second look-endoscopy (with second-look endoscopy vs without, 65.4% vs 47.8%; $p = 0.003$) although the data were unknown in 71 patients with 77 lesions. Histology, depth of invasion, macroscopic appearance, location of the tumor, specimen size, procedure time, ulcer, and use of antiplatelet agents or anticoagulants did not differ between the both groups.

Almost all the second-look endoscopies were performed on 2 days after ESD (160 lesions, 97.0%). Remaining two and three lesions underwent second-look endoscopy on 1 and 3 days after ESD, respectively.

2. Comparative clinical outcomes of ESD based on implementation of second-look endoscopy

Clinical outcomes and complications of ESD are shown in Table 2. The *en bloc* resection rate was higher in the patients with second-look endoscopy than in those without (with second-look endoscopy vs without, 99.4% vs 93.6%; $p = 0.003$). In contrast, complete resection rate and procedure time did not differ between the groups. When second-look endoscopy was conducted, prophylactic coagulation was performed in 35 lesions (21.2%). Delayed post-ESD bleeding developed in one of these 35 lesions (2.9%). In this case, bleeding occurred at the artificial ulcer but not at the site that had undergone prophylactic coagulation during second-look endoscopy. The bleeding site had been seen as a clean base during second-look endoscopy. In the 130 lesions (78.8%) in which prophylactic coagulation was not performed during second-look endoscopy, on the contrary, post-ESD bleeding occurred in four lesions (3.1%). In addition, the overall delayed post-ESD bleeding rate did not differ be-

Table 1. Patient and Lesion Characteristics

Variable	With second-look endoscopy	Without second-look endoscopy	p-value
No. of patients	140	267	
No. of lesions	165	280	
Age, yr*	62.7±9.2	64.5±8.7	0.047
Sex*			0.204
Male	100 (71.4)	206 (77.2)	
Female	40 (28.6)	61 (22.8)	
Underlying disease*			
Hypertension	52 (37.1)	127 (47.6)	0.044
Coronary heart disease	12 (8.6)	27 (10.1)	0.616
Cerebrovascular disease	6 (4.3)	5 (1.9)	0.199
Diabetes	18 (12.9)	50 (18.7)	0.132
Chronic kidney disease	4 (2.9)	4 (1.5)	0.455
<i>Helicobacter pylori</i> infection**†			0.003
Presence	68 (65.4)	111 (47.8)	
Absence	36 (34.6)	121 (52.2)	
Histology			0.785
Low grade dysplasia	77 (46.7)	118 (42.1)	
High grade dysplasia	21 (12.7)	42 (15.0)	
Differentiated carcinoma	60 (36.4)	109 (38.9)	
Undifferentiated carcinoma	7 (4.2)	11 (3.9)	
Depth of invasion in early gastric cancer‡			0.600
Mucosa	53 (79.1)	101 (84.2)	
Submucosa <500 µm	4 (6.0)	7 (5.8)	
Submucosa ≥500 µm	10 (14.9)	12 (10.0)	
Macroscopic appearance			0.331
Elevated	137 (83.0)	236 (84.3)	
Flat	8 (4.8)	20 (7.1)	
Depressed	20 (12.1)	24 (8.6)	
Location			0.124
Upper third	8 (4.8)	29 (10.4)	
Middle third	35 (21.2)	58 (20.7)	
Lower third	122 (73.9)	193 (68.9)	
Specimen size, mm			0.094
≤30	53 (32.1)	119 (42.5)	
31–40	78 (47.3)	111 (39.6)	
>40	34 (20.6)	50 (17.9)	
Presence of ulcer before ESD	3 (1.8)	5 (1.8)	>0.999
Use of antiplatelet agents or anticoagulants§	41 (24.8)	79 (28.2)	0.440

Data are presented as number (%) or mean±SD.

ESD, endoscopic submucosal dissection.

*This variable was calculated based on the number of patients; †*Helicobacter pylori* infection status was unknown in 71 patients; ‡This ratio was expressed as the percentage of patients with early gastric cancer; §Antiplatelet agents or anticoagulants included aspirin, nonsteroidal anti-inflammatory drugs, and warfarin. All patients discontinued these drugs before ESD. 'Use of antiplatelet agents or anticoagulants' indicates the number of the patients who took those medications on a usual day, not during ESD.

tween the groups (with second-look endoscopy vs without, 3.0% vs 2.1%; p=0.546).

Ten of the 11 lesions of post-ESD bleeding were controlled

by endoscopic therapy, while one lesion in which it failed was treated successfully with arterial embolization.

In order to assess skill of the endoscopists, we further re-

Table 2. Clinical Outcome and Complication of Endoscopic Submucosal Dissection

Variable	With second-look endoscopy	Without second-look endoscopy	p-value
<i>En bloc</i> resection	164 (99.4)	262 (93.6)	0.003
Complete resection	157 (95.2)	269 (96.1)	0.643
Procedure time, hr			0.428
<1	126 (76.4)	226 (80.7)	
1–2	31 (18.8)	44 (15.7)	
2–3	8 (4.8)	8 (2.9)	
≥3	0	2 (0.7)	
Prophylactic hemostasis during second-look endoscopy	35 (21.2)	NA	NA
Injection of hypertonic saline–epinephrine solution*	1 (2.9)	NA	NA
Thermocoagulation*	35 (100.0)	NA	NA
Hemoclipping*	1 (2.9)	NA	NA
Delayed post-ESD bleeding	5 (3.0)	6 (2.1)	0.546
Bleeding required blood transfusion [†]	4 (80.0)	3 (50.0)	0.545
Hemostatic method for delayed post-ESD bleeding [†]			0.455
Arterial embolization	1 (20.0)	0	
Emergency endoscopy	4 (80.0)	6 (100.0)	
Injection of hypertonic saline–epinephrine solution	0	2 (33.3)	0.467
Thermocoagulation	4 (100.0)	4 (66.7)	0.467
Hemoclipping	1 (25.0)	2 (33.3)	>0.999
Successful hemostasis for delayed post-ESD bleeding [†]	5 (100.0)	6 (100.0)	NA
Total	165	280	

Data are presented as number (%).

NA, not applicable; ESD, endoscopic submucosal dissection.

*This ratio is expressed as the percentage of the lesions requiring prophylactic hemostasis during a second-look endoscopy; [†]This ratio is expressed as the percentage of the lesions in which delayed post-ESD bleeding developed.

Table 3. Excluded Lesions Due to Complications

Variable	Endoscopists who performed second-look endoscopy routinely	Endoscopists who did not perform second-look endoscopy	p-value
Perforation	7 (4.0)	15 (4.9)	0.660
Immediate post-ESD bleeding	5 (2.8)	9 (3.0)	>0.999
Total*	177	304	

Data are presented as number (%).

NA, not applicable; ESD, endoscopic submucosal dissection.

*In total, there were 22 lesions with perforation and 14 lesions with immediate post-ESD bleeding, and 445 lesions were included in this study.

viewed the excluded lesions due to perforation and immediate post-ESD bleeding (Table 3). Perforation rate of endoscopists who performed second-look endoscopy routinely was 4.0% and that of endoscopists who did not perform second-look endoscopy was 4.9% ($p=0.660$). Immediate bleeding rates also were not different between two endoscopists group ($p>0.999$).

3. Factors related to delayed post-ESD bleeding

The factors associated with delayed post-ESD bleeding are shown in Table 4. In univariate analysis, cerebrovascular disease history and specimen size was associated with delayed post-

ESD bleeding. Multivariate analysis demonstrated that tumors in the upper third of the stomach (odds ratio [OR], 5.353; 95% confidence interval [CI], 1.075 to 26.650) and a specimen size greater than 40 mm (OR, 4.794; 95% CI, 1.307 to 17.588) were independent risk factors for delayed post-ESD bleeding. Second-look endoscopy, however, was not related to delayed post-ESD bleeding (OR, 1.789; 95% CI, 0.483 to 6.633).

Fig. 2 shows the relationship between postoperative day and post-ESD bleeding. Post-ESD bleeding most often developed on the first day after ESD. However, these lesions were excluded in this study. Delayed post-ESD bleeding occurred in 11 lesions (five

Table 4. Univariate and Multivariate Analysis of Delayed Post-Endoscopic Submucosal Dissection Bleeding

Variable	No.	Delayed post-ESD bleeding	Univariate	Multivariate		
			p-value	OR	95% CI	p-value
Age, yr			0.632			
<65	234	5 (2.1)		1.000		
≥65	211	6 (2.8)		0.718	0.182–2.831	0.636
Sex			0.074			
Male	338	11 (3.3)		1.000		
Female	107	0		<0.001	NA	0.996
Underlying disease						
Hypertension	197	4 (2.0)	0.762			
Coronary heart disease	47	1 (2.1)	>0.999			
Cerebrovascular disease	15	2 (13.3)	0.049	3.790	0.600–23.942	0.157
Diabetes	76	2 (2.6)	>0.999			
Chronic kidney disease	11	0	>0.999			
<i>Helicobacter pylori</i> infection*	19	4 (2.1)	>0.999			
Histology			0.901			
Low grade dysplasia	195	5 (2.6)				
High grade dysplasia	63	2 (3.2)				
Differentiated dysplasia	169	4 (2.4)				
Undifferentiated dysplasia	18	0				
Depth of invasion in early gastric cancer			>0.999			
Mucosa	154	4 (2.6)				
Submucosa <500 μm	11	0				
Submucosa ≥500 μm	22	0				
Macroscopic appearance			0.300			
Elevated	373	8 (2.1)				
Flat	28	1 (3.6)				
Depressed	44	2 (4.5)				
Location			0.073			
Upper third	37	3 (8.1)		5.353	1.075–26.650	0.040
Middle third	93	2 (2.2)		1.127	0.209–6.063	0.889
Lower third	315	6 (1.9)		1.000		
Specimen size, mm			0.038			
≤40	361	6 (1.7)		1.000		
>40	84	5 (6.0)		4.794	1.307–17.588	0.018
Ulcerative lesion before ESD			>0.999			
Absent	437	11 (2.5)				
Present	8	0				
Procedure time, hr*			0.253			
<1	352	7 (2.0)				
≥1	93	4 (4.3)				
Previous use of antiplatelet agents or anticoagulants			0.176			
No	325	6 (1.8)		1.000		
Yes	120	5 (4.2)		2.153	0.526–8.805	0.286
Second-look endoscopy			0.546			
Without	280	6 (2.1)		1.000		
With	165	5 (3.0)		1.789	0.483–6.633	0.384

Data are presented as number (%).

ESD, endoscopic submucosal dissection; OR, odds ratio; CI, confidence interval; NA, not applicable.

**Helicobacter pylori* infection status was unknown in 77 lesions.

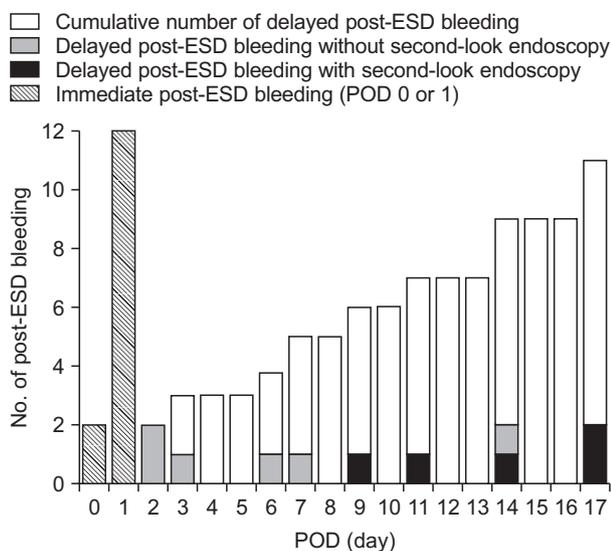


Fig. 2. Post-endoscopic submucosal dissection (ESD) bleeding lesions. POD, postoperative day.

lesions with second-look endoscopy and six lesions without). Delayed post-ESD bleeding in the patients who did not undergo second-look endoscopy occurred significantly earlier than that of the patients who underwent second-look endoscopy (median duration between ESD and the post-ESD bleeding: with second-look endoscopy vs without, 14.0 days vs 4.5 days, respectively; $p=0.022$).

DISCUSSION

Endoscopic resection has been an alternative treatment option for patients with gastric neoplasms including gastric adenomas and EGCs.^{1,5} Patients who undergo endoscopic resection have an excellent prognosis, with a 5-year survival rate of over 90%.¹⁹ In contrast to the conventional EMR technique that is inadequate for *en bloc* resection of lesions, especially large lesions, ESD allows the complete resection of both large and ulcerated lesions.^{3,4} However, bleeding after ESD occurs more frequently than after the conventional EMR technique.²⁰ Therefore, in order to prevent post-ESD bleeding, second-look endoscopies are performed at many institutions.²¹ However, there is little information as to whether a post-ESD second-look endoscopy lowers the post-ESD bleeding rate. Goto *et al.*²² reported that the maximum post-ESD bleeding rates before and after second-look endoscopy were not significantly different. In addition, they concluded that a second-look endoscopy after gastric ESD may contribute little to the prevention of delayed bleeding. In their study, however, most patients (98.9%) underwent second-look endoscopy after ESD. Therefore, pure comparison between the groups with and without second-look endoscopy was impossible. In addition, one prospective randomized controlled study demonstrated that second-look endoscopy did not reduce post-

ESD bleeding.²³ However, power of the test in the study was too weak due to small sample size (91 patients per group). Further study with larger sample size was needed to valid that second-look endoscopy would not reduce post-ESD bleeding.

We compared 165 lesions that underwent a second-look endoscopy with 280 lesions that did not. *En bloc* resection rate in our study was higher in the patients with second-look endoscopy than in those without. This was due to a difference of *en bloc* resection rates among the different endoscopists. However, complete resection and ESD procedure time did not differ between the two groups. Moreover, perforation and immediate post-ESD bleeding rates did not differ between endoscopists who performed second-look endoscopy routinely and those who did not. Because all of these complications, perforation and immediate post-ESD bleeding, developed within 2 days irrespective of performing of second-look endoscopy, we could consider that level of skill did not differ between two endoscopists' groups.

In multivariate analysis for delayed post-ESD bleeding, performing a second-look endoscopy was not related to less delayed post-ESD bleeding. This finding suggests that a post-ESD second-look endoscopy in patients without signs of bleeding may not be useful. However, other clinical factors including tumor location and specimen size were found to be associated with post-ESD bleeding. In line with our results, previous studies revealed that a specimen size greater than 40 mm is an independent risk factor for post-ESD bleeding.^{9,24} Moreover, other reports also showed that bleeding occurred more frequently in the corpus than in the antrum.^{25,26} Okada *et al.*⁹ demonstrated the tumor located in the middle third of the stomach was an independent risk factor for post-ESD bleeding on the fifth day or later after ESD. However, the relationship between tumor location and post-ESD bleeding remains controversial to date. In addition, many previous studies reported that PPI can be an influential factor for the prevention of post-ESD bleeding.²⁷⁻²⁹ In our study, however, PPI was administered to all patients at least 4 weeks with standard dose, and all post-ESD bleeding events developed within 17 days from ESD. Therefore, usage of PPI did not influence to post-ESD bleeding.

Besides tumor location in the upper third of the stomach, which is a difficult location in which to perform ESD, various factors including patient's underlying disease and drug history, endoscopist's experience, and preventive coagulation of visible vessels in the resection area after ESD may affect post-ESD bleeding.^{7,8,30-33} Higashiyama *et al.*⁸ reported that patients undergoing dialysis were at high risk for post-ESD bleeding. In contrast to patients with end-stage renal disease, Kwon *et al.*³¹ showed that post-ESD bleeding was not increased in patients with chronic renal failure or cirrhosis. The safety of continuous administration of antiplatelet agents in peri-ESD procedures is also controversial. Lim *et al.*²⁴ demonstrated that continuous administration of anti-platelet agent was not an independent risk factor for post-ESD bleeding. However, the European Society of

Gastrointestinal Endoscopy guideline, published in 2011, recommended discontinuation of aspirin for 5 days in patients with low thrombotic risk.³³ A recent Korean study also showed that continuous aspirin use increased the risk of post-ESD bleeding.³² Whether antiplatelet agents should be discontinued before ESD has been a debated issue because previous guidelines are based on observation studies, expert opinions, and best clinical practices and are rarely supported by prospective or randomized controlled trials.³⁴ Regrettably, we could not analyze the effect of antiplatelet agent on post-ESD bleeding because all the patients in our study who underwent ESD discontinued antiplatelet agent use. Although the usefulness of second-look endoscopy was not demonstrated in our study, selective second-look endoscopy in patients at high risk for post-ESD bleeding may be considerable and cost-effective. Additional prospective studies are needed to prove whether this approach is useful.

In our results, prophylactic hemostasis was performed in 35 lesions during second-look endoscopy. Of these, one (2.9%) developed delayed post-ESD bleeding, though at a site different from the original site of the prophylactic hemostasis. In the 130 lesions that did not have prophylactic hemostasis because no stigmata was observed in the second-look endoscopy, four (3.1%) developed post-ESD bleeding. These results support the notion that second-look endoscopy may not be important in reducing delayed post-ESD bleeding.

Because the patients who underwent ESD were usually discharged on 2 days after ESD and endoscopists concerned about delayed post-ESD bleeding after the patients were discharged, second-look endoscopy was performed just before being discharged. Therefore, almost of the second-look endoscopies were not performed on the next day after ESD but did on 2 days after ESD. Performing a second-look endoscopy on 2 days after ESD was enough to evaluate whether second-look endoscopy can prevent a delayed post-ESD bleeding. However, we could not analyze relationship between second-look endoscopy and immediate post-ESD bleeding which occurred within 1 day after ESD. In our study, immediate post-ESD bleeding developed at 14 lesions (Fig. 2), which are relatively large number compared with that of delayed post-ESD bleeding. Although this study focused on the delayed post-ESD bleeding, immediate post-ESD bleeding is also one of the endoscopist's major concerns. We plan to perform a second-look endoscopy on the next day after ESD in the subsequent study for identifying the relationship between second-look endoscopy and immediate post-ESD bleeding.

An interesting finding of the present study is that delayed post-ESD bleeding which developed within 1 week occurred only in the patients who did not undergo second-look endoscopy. On the other hand, delayed post-ESD bleeding which developed after 1 week from ESD occurred mainly in the patients who underwent a second-look endoscopy. Although this is too few lesions of bleeding to draw a definite conclusion, delayed

post-ESD bleeding of the patients who did not undergo second-look endoscopy occurred significantly earlier. A large scale study may be required to validate this result.

Our study has several limitations. First, even though almost data were collected prospectively for future analysis of ESD performance, the patients undergoing second-look endoscopy were reviewed retrospectively. Secondly, we allocated the patients to two groups based on the endoscopists rather than computerized random method. Therefore, there may be a bias according to the doctor who performed the ESD. All endoscopists, however, were experts who had performed 300 cases or more of ESD, and we demonstrated that level of endoscopists' skill was not different between two endoscopists' groups, indirectly, through evaluation of perforation and immediate post-ESD bleeding rates. Therefore, the bias from endoscopists was minimal. Thirdly, a fair number of post-ESD bleedings, which developed within 1 day from ESD, were excluded because most second-look endoscopies were performed on the second day after ESD. If we had a purpose of including as many post-ESD bleedings as possible, second-look endoscopies should be performed on the following day from ESD. However, our concern was whether second-look endoscopy which was performed just before the discharge could reduce delayed post-ESD bleeding after the discharge. In the present study, therefore, delayed post-ESD bleeding was defined as the bleeding which occurred at ESD site after 2 days from ESD, as mentioned in methods. In addition, almost second-look endoscopies were performed on the second day from ESD.

In conclusion, a second-look endoscopy did not reduce the risk of delayed post-ESD bleeding after gastric ESD. Therefore, a routine second-look endoscopy after gastric ESD might not be necessary for all patients to prevent delayed post-ESD bleeding.

CONFLICTS OF INTEREST

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

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