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Second and Third-look Endoscopy for the Prevention of Post-ESD Bleeding

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Abstract: The efficacy of 2nd-look esophagogastroduodenoscopy (EGD) with endoscopic hemostatic therapy (EHT) for the prevention of postendoscopic submucosal dissection (ESD) clinical bleeding remains controversial. The aim of this study was to estimate post-ESD bleeding rate using 2nd and 3rd-look strategy, and to determine risk factors for clinical bleeding, and for EHT at 2nd and 3rd-look EGDs.

Three hundred forty-four consecutive patients with early gastric cancer or adenoma underwent ESD from January 2006 through March 2012. Second and 3rd-look EGDs were performed on day 1 (D1) and day 7 (D7), respectively, with EHT as needed.

Post-ESD clinical bleeding rate was 2.6% (95% confidence interval [CI] 1.2%–4.9%). For clinical bleeding, adjusted odds ratios (ORs) for age <65 years and antithrombotic drug uses were 4.40 (95% CI 1.07–19.93) and 7.34 (95% CI 1.80–32.48), respectively. For D1 EHT, adjusted ORs of tumor location in the lower part of the stomach and maximum tumor diameter ≥60 mm were 2.16 (95% CI 1.35–3.51) and 2.20 (95% CI 1.05–4.98), respectively. For D7 EHT, adjusted OR of D1 EHT was 4.65 (95% CI 1.56–20.0).

Post-ESD clinical bleeding rate was relatively low using 2nd and 3rd-look strategy. Age <65 years and antithrombotic drug use are significant risk factors for clinical bleeding. Regarding EHT, tumor location in the lower part of the stomach and maximum diameter of resected specimen ≥60 mm are significant predictors for D1 EHT. D1 EHT in turn is a significant risk factor for D7 EHT. The efficacy of sequential strategy for preventing post-ESD bleeding is promising.

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Abbreviations: CI = confidence interval, D1 = day 1, D7 = day 7, EGCs = early gastric cancers, EGD = esophagogastroduodenoscopy, EHT = endoscopic hemostatic therapy, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, L = lower, M = middle, Mu = mucosal, ORs = odds ratios, RCT = randomized controlled trial, Sm = submucosal, U = upper.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is a common and established therapy used for the treatment of superficial lesions including early cancer, adenoma, and high-grade dysplasia of the gastrointestinal tract.[1] Advantages of ESD include a higher rate of en-bloc resection for larger lesions followed by accurate determination of tumor depth and margin, as well as a higher rate of complete resection compared with endoscopic mucosal resection (EMR), and a reduced risk of tumor recurrence.[2,3] ESD requires special equipment and is more technically challenging than conventional EMR.[4]

Bleeding is a serious, albeit expected, adverse event associated with ESD. Clinical bleeding after ESD was reported to be 4.53% in a previous meta-analysis.[5]

It is reported that the stigmata of scheduled 2nd-look esophagogastroduodenoscopy (EGD) with/without endoscopic hemostatic therapy (EHT) is significantly associated with subsequent clinical bleeding,[6,7] but a recent randomized controlled trial (RCT) suggested no significant benefit of 2nd-look EGD for preventing clinical bleeding after ESD.[8] There have been no studies investigating the preventive effectiveness of 2nd and 3rd-look EGDs on day 1 (D1) and day 7 (D7) for the prevention of post-ESD clinical bleeding. In addition, there is only 1 report describing predictors for EHT after gastric ESD.

The aims of this study were to estimate the rate of post-ESD clinical bleeding using 2nd and 3rd-look EGDs with/without EHT and to determine risk factors for clinical bleeding and for need of EHT during EGD after gastric ESD.

MATERIALS AND METHODS

Patients

A total of 441 patients underwent ESD from January 2006 through March 2012 at a tertiary referral university hospital in Japan. Of these, 71 of 441 patients had multiple neoplastic lesions and underwent ESD repeatedly during this period; only first ESD was included in our analysis in these 71 patients. On the remaining 370 index patients, 26 without 2nd or 3rd-look EGDs were excluded. This retrospective cohort study was conducted using the remaining 344 consecutive patients (Figure 1) who were hospitalized until D7. Among these patients, a total of 344 gastric epithelial neoplasms were identified, including 276 early gastric cancers (EGCs) and 68

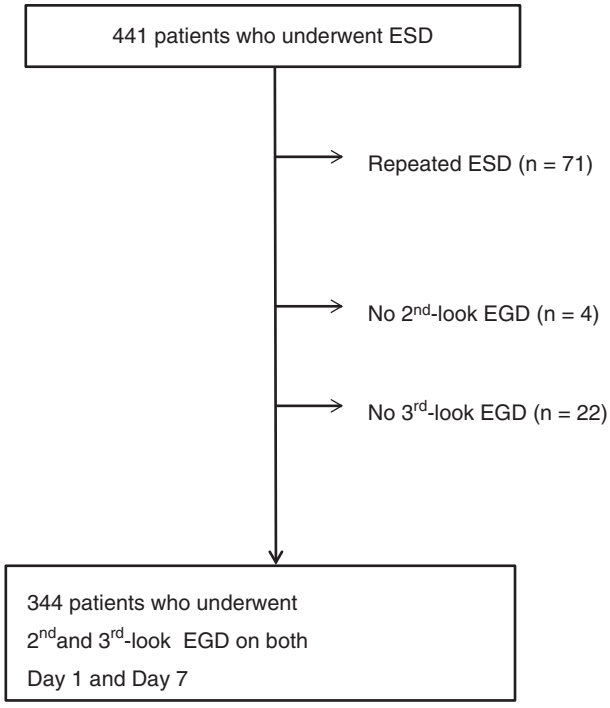

FIGURE 1. Study flow diagram. A total of 441 patients underwent ESD. Seventy-one patients of 441 had multiple neoplastic lesions and underwent ESD repeatedly in this period. Twenty-six of these 370 patients did not undergo either 2nd or 3rd-look EGD. This retrospective cohort study was conducted using the remaining 344 consecutive patients. EGD = esophagogastroduodenoscopy, ESD = endoscopic submucosal dissection.

adenomas. Second and 3rd-look EGDs were performed on D1 and D7, respectively. Indications for ESD were determined as per guidelines proposed by the Japanese Gastric Cancer Association with expanded criteria, as follows: differentiated adenocarcinoma with no apparent findings of submucosal invasion or ulcer with any tumor size, or size <30 mm if with ulcer findings; undifferentiated adenocarcinoma with no apparent findings of submucosal invasion or ulcer, with diameter <20 mm.[9]

Anticoagulants (warfarin in 10 patients) were discontinued and restarted following American Society for Gastrointestinal Endoscopy guidelines.[10] One patient with a history of pulmonary embolism received bridging therapy using heparin during interruption of warfarin administration. Warfarin and clopidogrel were restarted on D1 after confirming hemostasis. There was no patient who was taking both warfarin and clopidogrel. Fifty-three patients were taking aspirin or other antiplatelet agents, including thienopyridines. Administration of these drugs was suspended for 7 days prior to ESD and restarted after D8.

ESD Procedure

Informed consent was obtained from all patients prior to ESD. Ten milligrams of rabeprazole was administered for 3 days prior to ESD and for 8 weeks after ESD. All procedures were performed under conscious sedation using diazepam and pethidine. A single-channel endoscope with/without water jet (GIF-Q240, GIF-Q260J; Olympus, Tokyo, Japan) or a 2-channel multibending endoscope (GIF-2TQ260 M; Olympus) was used with high-frequency power supply unit (VIO300D; ERBE, Tübingen, Germany) for electrocoagulation, needle-knife (KD-10Q-1; Olympus), and an insulated-tip (IT)-Knife (KD-610L, KD-611L; Olympus).

The steps of ESD were as follows. First, several spots were marked 5 to 10 mm outside of the tumor edge using the needle knife. All marks were confirmed to be outside of tumor using a magnifying endoscope. Second, after injection of saline or 10% glycerin solution mixed with sodium hyaluronate (MucoUp®; Johnson & Johnson Medical Company, Tokyo, Japan) and 0.0025% epinephrine into the submucosa around the lesion, an initial mucosal incision was made 5 mm outside the spots with the needle knife. Third, ESD was performed using the IT-Knife after incision of the mucosa. Fourth, all visible vessels on the ulcer base were coagulated by hemostatic forceps (Coagrasper, FD-410LR; Olympus) after resection of the lesion.

Resected specimens were spread and pinned on flat rubber plates for length and width measurement immediately after the procedure.

Second and 3rd-look EGDs and Follow-up After ESD

Second and 3rd-look EGDs were performed on D1 and D7 to evaluate post-ESD ulcer and to perform EHT if needed. If active bleeding or nonbleeding visible vessels were observed, those lesions were coagulated with hemostatic forceps. Hemostatic procedures were performed on visible vessels with/without blood clots to prevent possible future ulcer bleeding even in the absence of active bleeding. In other words, EHT was performed under conditions equivalent to Forrest classification[11] Ia, Ib, and IIa of bleeding peptic ulcer disease.

After confirming hemostasis by EGD on D1, patients started a light meal on day 2. Patients with spurting bleeding or difficult hemostasis on 2nd-look EGD started meals on day 3. All patients were carefully observed for hematemesis, melena or hemoglobin change during hospitalization. Emergent endoscopy was performed if clinical bleeding was suspected. Clinical bleeding was defined as active bleeding requiring additional emergent EGD with EHT. We categorized clinical bleeding as either early (before D7) or late (after D7).

After discharge, follow-up endoscopy at 8 weeks was scheduled for all patients to evaluate ESD ulcer healing. Patients were asked to return to the hospital if they developed any signs of bleeding such as melena or hematemesis.

Candidate Predictors for Clinical Bleeding and EHT on 2nd and 3rd-look EGDs

The 344 patients were divided by clinical bleeding and the need for additional EHT on D1 and D7. Clinical relevant data including age, sex, antithrombotic medication (antiplatelet and/or anticoagulation drugs) platelet and/or anticoagulant drug use, tumor location, macroscopic findings of tumor, size of resected specimens, tissue diagnosis, pathological tumor depth, ulcer bleeding site, and need for EHT on D1 and D7 were collected.

Tumor location was reported according to the Japanese Classification of Gastric Cancer, with the stomach anatomically divided into upper (U), middle (M), and lower (L) parts by the lines connecting the points trisecting the lesser and greater curvatures, respectively.[12] The maximum diameter of the resected specimen was divided into 3 categories: <30 mm, 30 to <60 mm, or ≥60 mm. Endoscopic findings of EGC were reported following per the Japanese Classification of Gastric Cancer criteria.[12] The macroscopic appearance of

EGC (type 0, T1 of TNM classification) was divided into 2 categories: type 0-I, protruding and Type 0-II, superficial. Type 0-II was further subdivided into 3 categories: Type 0-IIa, superficial elevated; Type 0-IIb, superficial flat; and Type 0-IIc, superficial depressed. We pooled Type 0-I and Type 0-IIa together as elevated lesions, whereas Type 0-IIb and 0-IIc were combined as depressed lesions. All resected specimens were microscopically examined after cutting into 2 to 3-mm slices. Tissue diagnosis included adenoma and adenocarcinoma. Tumor depth was classified as extension into the mucosal (Mu) or submucosal (Sm) layer.

All study protocols were approved by the Institutional Review Board at our hospital.

Statistical Analysis

Fisher's exact test was used for comparison of proportions, whereas Student's *t* test was used for continuous variables. Bivariate and multivariate logistic regression analyses were subsequently performed. All analyses including confidence intervals were 2-sided, and type I error <0.05 was considered statistically significant. All statistical analyses were performed using JMP version 10 statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

The mean age (standard deviation) of patients was 70.6 (8.4) years and 259 patients (75%) were male. The median size of resected specimens (range) was 38.0 mm (15–92). Sixty-three patients (18.3%) were taking antithrombotics, which were stopped prior to the procedure. Macroscopically, 156 lesions (45.3%) were elevated, and the remaining 188 lesions (54.7%) were depressed. Regarding the depth of lesions, 303 lesions (88.1%) were microscopically diagnosed as Mu, whereas 41 lesions (11.9%) were diagnosed as Sm or deeper (Table 1). Perforation during ESD occurred in 7 patients. These patients were treated conservatively with endoscopic clipping and intravenous antibiotics. One patient required blood transfusion due to profound bleeding during the procedure. No patients required surgical treatment for complications of ESD (Table 1).

TABLE 1. Baseline Characteristics of the 344 Study Participants

Age, mean (SD)	70.6 (8.4)
Male sex, n (%)	259 (75.3)
Antithrombotic drugs use, n (%)	63 (18.3)
Lesions characteristics	
Resected specimen size, median (range)	38.0 (15–92)
Tumor size, median (range)	16.0 (2–77)
Tumor location	
Upper, n (%)	55 (16.0)
Middle, n (%)	144 (41.9)
Lower, n (%)	145 (42.1)
Macroscopic findings	
Elevated type, n (%)	156 (45.3)
Depressed type, n (%)	188 (54.7)
Pathological tumor depth	
Mucosal layer, n (%)	303 (88.1)
Submucosal layer, n (%)	41 (11.9)
Tissue diagnosis	
Adenoma, n (%)	68 (19.8)
Adenocarcinoma, n (%)	276 (80.2)
Resectability	
En-bloc resection, n (%)	341 (99.2)
Procedure-related complication	
Clinical bleeding*, n (%)	9 (2.6)
Blood transfusion, n (%)	1 (0.29)
Perforation, n (%)	7 (2.0)

n = number of patients, SD = standard deviation.
* Clinical bleeding was defined as active bleeding requiring additional emergent esophagogastroduodenoscopy with endoscopic hemostatic therapy.

Bi- and Multivariate Analysis for Clinical Bleeding and the Need for EHT on D1 and D7

Nine cases developed clinical bleeding. The rate of clinical bleeding was 2.6% (95% confidence interval [CI] 1.2%–4.9%). All 9 cases required EHT on emergent EGD, in addition to scheduled 2nd and 3rd-look EGDs. Six of 9 cases developed early clinical bleeding, whereas the remaining 3 cases had late bleeding (Table 2). Five of 6 early bleeding cases developed clinical bleeding, though they underwent EHT on D1. The first late clinical bleeding patient who also required EHT on D1 had chronic myelomonocytic leukemia with mild thrombocytopenia (platelet count around 10×10^4 cells/μL). Clinical bleeding developed around midnight on D7 after 3rd-look EGD without EHT. The second late bleeding case had been taking aspirin for cardiovascular disease. Aspirin was restarted on day 8, with clinical bleeding on day 11. The third late bleeding case did not have any comorbidity. EHT was performed on neither D1 nor D7, but clinical bleeding developed on day 11.

For clinical bleeding, adjusted odds ratios (ORs) of age <65 years and antithrombotic drug uses were 4.40 (95% CI 1.07–19.93) and 7.34 (95% CI 1.80–32.46), respectively.

For D1 EHT, adjusted ORs of tumor location in the lower part of the stomach, maximum diameters ≥ 30 mm, ≥ 60 mm for EHT were 2.16 (95% CI 1.35–3.51), 1.34 (95% CI 0.75–2.39), and 2.20 (95% CI 1.05–4.98), respectively. For D7 EHT, adjusted OR of D1 EHT was 4.65 (95% CI 1.56–20.0) (Table 3).

142 cases (64.3%) of EHT on D1 were due to non-bleeding visible vessels. In contrast, 21 (77.8%) cases of EHT on D7 were due to active bleeding (oozing and spurting) (Table 4).

DISCUSSION

Our study showed that clinical bleeding rate was relatively low using 2nd and 3rd-look follow-up EGDs. Age <65 years and antithrombotic drug use are significant risk factors for clinical bleeding. Tumor location in the lower part of the stomach and a maximum size of the resected specimen ≥ 60 mm are significant risk factors for EHT on D1. D1 EHT is a significant risk factor for EHT on D7.

Goto et al[14] conducted a multicenter survey of management after gastric ESD in Japan. They reported that 2nd-look EGD after gastric ESD is performed in almost all cases in several tertiary referral centers in Japan and that frequency of postoperative bleeding, equivalent to clinical bleeding in our study, was not associated with the institutional-level proportion of gastric ESD patients who underwent 2nd-look EGD.

Second-look EGD is not routinely recommended according to the guidelines for treatment of bleeding peptic ulcer

TABLE 2. Analysis of the 344 Patients Who Underwent 2nd and 3rd-look EGDs

	Day 1 After ESD			Day 7 After ESD			Observation Until 2 Months' Follow-up		
	EHT (n = 221)	No EHT (n = 123)	*P* value	EHT (n = 27)	No EHT (n = 317)	*P* value	Clinical bleeding (n = 9)	No clinical bleeding (n = 335)	*P* value
Age, mean (SD)	70.9 (8.7)	70.0 (7.9)	0.38	67.5 (10.5)	70.9 (8.2)	0.046	67.6 (11.7)	70.4 (8.4)	0.28
Male sex, n (%)	168 (76.0)	91 (74.0)	0.68	20 (74.1)	239 (75.4)	0.88	8 (88.9)	251 (74.9)	0.46
Antithrombotic drugs use, n (%)	43 (19.5)	20 (16.3)	0.46	3 (11.1)	60 (18.9)	0.44	5 (55.6)	58 (17.3)	0.012
Resected specimen size, mean (SD)	41.7 (13.9)	38.8 (13.5)	0.066	43.4 (12.8)	40.5 (13.9)	0.3	42.1 (13.2)	40.7 (13.8)	0.76
Tumor location of lower part stomach, n (%)	106 (48.0)	39 (31.7)	0.0034	14 (51.9)	131 (41.3)	0.29	0 (0)	145 (43.3)	1
Macroscopic findings of depressed, n (%)	120 (54.3)	68 (55.3)	0.86	19 (70.4)	169 (53.3)	0.087	7 (77.8)	181 (54.0)	0.19
Pathological tumor depth of submucosal layer, n (%)	23 (10.4)	18 (14.6)	0.25	2 (7.4)	39 (12.3)	0.45	1 (11.1)	40 (11.9)	1
Tissue diagnosis of adenocarcinoma, n (%)	171 (77.4)	105 (85.4)	0.075	22 (81.5)	254 (80.1)	0.87	8 (88.9)	268 (80.0)	1
EHT on Day 1 after ESD, n (%)	–	–	–	24 (88.9)	197 (56.7)	0.0056	6 (66.6)	215 (64.2)	1

EHT = endoscopic hemostatic therapy, ESD = endoscopic submucosal dissection, n = number of patients, SD = standard deviation.

disease.[13] However, evidence-based strategy regarding the use of 2nd-look EGD after ESD has yet to be established. Ryu et al[8] showed no efficacy of 2nd-look EGD for the prevention of clinical bleeding after ESD in a RCT reporting that 7 patients developed late clinical bleeding out of 21 post-ESD bleeding patients. Therefore, we assumed that 3rd-look EGD in addition to a 2nd-look EGD might be effective for preventing late post-ESD bleeding.

Several past studies reported risk factors for clinical bleeding. For example, Tsuji et al[15] reported an adjusted OR for clinical bleeding of 2.47 associated with tumor in lower third of stomach. Mannen et al[16] reported that adjusted ORs of resected size 31 to 50 mm and ≥51 mm were 2.72 (95% CI 1.04–7.11) and 9.22 (95% CI 3.48–24.5), respectively. Jang et al[17] reported significant association between cancer histology and clinical bleeding. Choi et al[7] reported that high risk of ulcer stigmata in 2nd-look EGD was a significant risk factor for clinical bleeding. Although our study did not show any statistically significant association with these factors, this might be due to type II error from the relatively small sample size.

Regarding predictors for EHT, Choi et al[7] reported that submucosal fibrosis and nausea are significant predictors for high-risk ulcers (Forrest I and IIa) on D1 on multivariate analysis. They found that tumor location and artificial ulcer diameter were relatively associated with high-risk ulcers needing EHT on D1 in bivariate analysis, but that these associations became nonsignificant on multivariate analysis. Our results regarding tumor location are compatible with their bivariate analysis.

Kaminishi et al[18] created a reflux model in rats in which total bile acid concentrations, intragastric pH, and serum gastrin were elevated, demonstrating that gastric ulcer healing may be substantially prolonged under these conditions. These results also support the hypothesis that antral location of lesion is a predictor for D1 high-risk ulcer.

Interestingly, the most common indication for EHT differed between EGDs done on D1 and D7, being nonbleeding visible vessels and active bleeding, respectively. This difference might be associated with the healing process of artificial ulcers. Takeuchi et al[19] reported that new capillary vessels developed into ulcer base on D7 in the model with acetic acid-induced gastric ulcer. These regenerating vessels might be associated with oozing or spurting on D7. It is notable that no <7 patients had active bleeding (spurting) on elective 3rd-look EGD.

The present study has strengths and limitations. This is the first study reporting the effectiveness of 2nd and 3rd-look EGDs with/without EHT for the prevention of post-ESD clinical bleeding. Additionally, there have been no reports investigating predictors for both D1 and D7's EHT. However, our study has several limitations. First, this is a single-arm observational study, and it is impossible to directly compare patients who had 2nd and 3rd-look EGD with patients who did not have follow-up EGD after ESD. Second, this was a retrospective study with its consequent information bias. Third, OR findings should be validated using other cohorts. Fourth, some measure of type II error is anticipated due to relatively small single-center study.

In conclusion, clinical bleeding is relatively rare using 2nd and 3rd-look EGDs after ESD. Age <65 years and antithrombotic drug use are significant risk factors for clinical bleeding. A substantial number of patients needed EHT at 2nd and 3rd-look EGDs. Tumor location in the lower part of the stomach and maximum diameter of the resected specimen ≥60 mm are significant risk factors for EHT at D1, which in turn, is a significant risk factor EHT at D7. The efficacy of 2nd and 3rd-look EGDs is promising and should be investigated via RCT in the future.

TABLE 3. Bi- and Multivariate Logistic Regression for EHT and Clinical Bleeding

	EHT on Day 1 After ESD						EHT on Day 7 After ESD						Clinical Bleeding					
	Bivariate			Multivariate			Bivariate			Multivariate			Bivariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age <65 years	1.05	0.63–1.72	0.85				0.45	0.20–1.05	0.06	0.48	0.21–1.15	0.10	3.66	0.95–15.09	0.059	4.43	1.07–19.93	0.041
Male sex	1.11	0.67–1.84	0.68				0.93	0.40–2.45	0.88				2.68	0.48–50.03	0.30			
Lower part of stomach	1.99	1.26–3.17	0.0032	2.16	1.35–3.51	0.0013	1.53	0.69–3.40	0.29				1.10	0.27–4.23	0.89			
Depressed type	0.96	0.62–1.50	0.86				2.08	0.91–5.17	0.082	1.81	0.76–4.62	0.18	2.98	0.71–20.20	0.14	2.19	0.49–15.30	0.32
Resected specimen size <30 mm	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–
≥30 mm	1.30	0.73–2.90	0.38	1.34	0.75–2.39	0.32	2.06	0.69–8.87	0.21	2.00	0.64–8.80	0.25	1.77	0.30–33.74	0.58			
≥60 mm	2.11	1.01–4.75	0.046	2.20	1.05–4.98	0.035	0.87	0.20–2.63	0.82	0.74	0.16–2.38	0.64	1.85	0.26–8.33	0.48			
Adenocarcinoma	0.59	0.31–1.04	0.069	0.56	0.30–1.00	0.051	1.09	0.43–3.36	0.86				2.0	0.36–37.42	0.48			
Sm invasion	0.68	0.35–1.33	0.25				0.57	0.09–2.02	0.42				0.92	0.05–5.22	0.94			
Antithrombotic drugs use	1.24	0.70–2.27	0.46				0.54	0.12–1.60	0.29				5.97	1.54–24.76	0.011	7.34	1.80–32.48	0.0064
EHT on Day 1 after ESD	–	–	–	–	–	–	0.20	0.05–0.60	0.0025	4.65	1.56–20.05	0.0028	1.11	0.29–5.36	0.88			

CI = confidence interval, EHT = endoscopic hemostatic therapy, ESD = endoscopic submucosal dissection, OR = odds ratio, Sm = submucosal layer.

TABLE 4. Findings of Post-ESD Ulcer That Needed EHT

	Day 1 After ESD	Day 7 After ESD
Total number of EHT patients, n, % (95% CI)	221, 64% (59–69)	27, 8%* (5–11)
Oozing, n, % (95% CI)	60, 27% (21–34)	14, 52% (32–71)
Spurting, n, % (95% CI)	19, 9% (5.1–13)	7, 26% (11–46)
Non-bleeding visible vessel, n, % (95% CI)	142, 64% (58–71)	6, 22% (8.6–42)

CI = confidence interval, EHT = endoscopic hemostatic therapy, ESD = endoscopic submucosal dissection.
* Twenty-four of 27 patients needed EHT on Day 1 after ESD.

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