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Communication

Clip Closure and PuraStat for Prevention of Clinically Significant Delayed Bleeding after Colorectal Endoscopic Submucosal Dissection: A Prospective, Observational Study

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Abstract: Background and aims. Clinically significant delayed bleeding (CSDB) may complicate endoscopic colorectal submucosal dissection (ESD). We aimed to assess the efficacy of preventive measures for CSDB. Methods. We assessed the results of a prospective registry of colorectal ESD for laterally spreading lesions. We evaluated the effect of clip closure and PuraStat application on the prevention of CSDB. Results. A total of 40 patients with 41 colorectal ESDs were included. ESD was successful in 38 lesions (92.7%), 35 with R0 resection (92.1%) and 33 with curative resection (86.8%). CSDB occurred in 3 of 38 lesions (7.9%, 95% CI [1.7–21.4%]), exclusively after rectal ESD (3 of 22 rectal lesions vs. 0 of 16 colonic lesions, $p = 0.249$). Clip closure was more frequently used after colonic ESD (12 of 16 colonic lesions vs. 2 of 22 rectal lesions, $p < 0.001$) and was not protective for CSDB in the univariate analysis, even though no events occurred after clip closure (0 of 14 lesions with clip closure vs. 3 of 24 lesions without, $p = 0.283$). PuraStat was more frequently applied after ESD for rectal lesions (16 of 22 rectal lesions vs. 2 of 16 colonic lesions, $p < 0.001$) and was not protective for CSDB, with all three events occurring after PuraStat application (3 of 18 lesions with PuraStat application vs. 0 of 20 lesions without, $p = 0.097$). Conclusions. CSDB occurred exclusively after rectal ESD, and no predictive factors were identified in the univariate analysis. Clip closure and PuraStat application were not protective for CSDB.

Keywords: endoscopic submucosal dissection; clip closure; PuraStat; delayed bleeding; muscle retracting sign; colorectal mixed adenoneuroendocrine carcinoma

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1. Introduction

Endoscopic submucosal dissection (ESD) has established itself as the main resection method for large adenomas, superficial adenocarcinomas and small-size neuroendocrine tumors (NETs) [1]. It has a steeper learning curve when compared to endoscopic mucosal resection (EMR), a higher curative rate and similar-to-higher rates of delayed bleeding and perforation [2].

A recent meta-analysis suggests that the prophylactic closure of colorectal mucosal defects after ESD could reduce the risk of delayed bleeding, an effect seen only in observational studies and not in randomized controlled trials [3]. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend against the prophylactic coagulation of visible vessels and do not recommend routine closure of the colorectal wall defect [2].

PuraStat is a synthetic self-assembled peptide gel that may be applied endoscopically on a bleeding site to achieve hemostasis. Although not recommended by current guidelines, the reported pooled rate for successful hemostasis is 93.1% with a rebleeding rate of 8.9% [4,5].

We aimed to assess the efficacy of clip closure and PuraStat application for clinically significant delayed bleeding (CSDB) after colorectal ESD.

2. Materials and Methods

We performed a post hoc analysis of a single-center prospectively maintained consecutive ESD registry (NCT06033976) with the Hospital Ethical Committee's approval (241564/01.04.2024). All patients diagnosed or referred to our department with non-pedunculated colorectal lesions above 20 mm in diameter in the period of January 2020 to April 2024 for whom ESD was deemed feasible were prospectively included. We also included residual endoscopic or surgical lesions, and lesions bordering on anastomosis or the dentate line, even if smaller than 20 mm.

Lesions were analyzed in white light and narrow-band imaging (NBI) using either a high-definition colonoscope for colonic lesions (CF H185L, Olympus, Tokyo, Japan) or a high-definition gastroscope for rectal lesions (GIF H185 or GIF 2TH180, Olympus, Japan) [6]. Their macroscopic appearance was expressed according to the Paris classification and as laterally spreading tumors (LST) if appropriate [7,8]. The surface of each lesion was examined and labeled according to the NBI International Colorectal Endoscopic (NICE) classification [1].

ESD was proposed for lesions classified as Paris Is, Paris IIa, NICE type 2 or NICE type 3 lesions in the lower rectum. Lesions classified as Paris Ip, Paris III or NICE type 1 were excluded. In addition, we performed complementary ESD of an endoscopic scar for a possible residual neuroendocrine tumor (NET) after non-curative EMR.

Anticoagulants and antiaggregants were discontinued before the procedures and resumed afterwards according to the latest ESGE guidelines [9]. A colloid solution was used for submucosal elevation (hydroxyethyl starch 500 mL + 1 mL adrenaline 1/1000 + 1 mL methylene blue). Incision and submucosal dissection were performed with ESD knives (Dual Knife J, IT Nano, Olympus, Japan) using electrocautery (ENDO CUT I and FORCED COAG modes, VIO 200D, ERBE, Tubingen, Germany). Hemostasis was conducted with knife and/or forceps (Coagrasper, Olympus, Japan). Snare resection was allowed, either to remove the lesion en bloc at the end (hybrid ESD) or to remove a part of the lesion that could not be dissected (piecemeal).

At the end of the procedure, vessels within the resection bed were prophylactically ablated with Coaggrasper, and any traces of blood within the colorectal lumen were thoroughly washed and aspirated. The resection bed was closed completely with metallic clips (Instinct Plus, Cook Medical, Bloomington, IN, USA) or a hemostatic peptide gel was evenly applied onto the wall defect (PuraStat, 3-D Matrix, Tokyo, Japan) in most cases.

Patients with hypertension were instructed to take their medication appropriately and maintain their blood pressure values towards the lowest normal values in the 14 days after the procedure.

CSDB was defined as post-ESD bleeding necessitating the prolongation of hospitalization or readmission, with a new endoscopic evaluation or a blood transfusion and occurring at least 6 h after the ESD [10].

Patients with non-curatively resected malignant lesions underwent complementary surgery or chemoradiotherapy [4].

Data recorded for categorical variables are expressed as absolute values and percentages. For normally distributed quantitative variables, data are presented and as means and standard deviations, or else medians and intervals. Univariate analysis was performed using Fisher's exact test for categorical variables and a T test for quantitative variables if normally distributed, and a Mann–Whitney U test otherwise. Odds ratios (ORs) were

presented with 95% confidence intervals (95% CI). SPSS 29.0 software (IBM, Endicott, NY, USA) was used for statistical analysis.

3. Results

We included 40 patients with 41 colorectal ESDs performed from 2020 to 2024. The characteristics of the patients and lesions are presented in Table 1. Of the 22 lesions in the rectum, one was contiguous to an ileo-rectal anastomosis, one was a residual scar after a non-curative endoscopic rectal NET resection and five were bordering the dentate line (2 of them residual after trans-anal surgery) (particular locations are given in Table 1).

Table 1. Patient and lesion characteristics.

Patients	40 patients
- Sex	22 men (55%)
- Age	63.9 ± 10.5 years
- Anticoagulants/antiaggregants	8 patients (29%)
Lesions	41 lesions
- Location	19 (46.3%) colon/22 (53.7%) rectum
(Colonic locations)	3 cecum/10 ascending/1 transverse/1 descending/4 sigmoid
(Particular locations)	1 ileo-rectal anastomosis/3 residual/5 dentate line
- Diameter *	37.5 mm (20–150)
- Paris type **	5 (12.5%) sessile (Paris Is)/35 (87.5%) LST (Paris 0-IIa)
(LST type)	
- NICE type **	13 LST-G-H/11 LST-G-MIX/4 LST-NG-F/7 LST-NG-PD
	37 (92.5%) NICE 2/3 (7.5%) NICE 3

LST-G-H, LST granular homogenous; LST-G-MIX, LST granular mixed-type; LST-NG-F, LST non-granular flat; LST-NG-PD, LST non-granular pseudo-depressed. * Excluding three rectal lesions measuring less than 20 mm—one of 15 mm bordering an ileo-rectal anastomosis, one 12 mm residual scar post surgery near the dentate line and one 10 mm residual scar post non-curative endoscopic rectal NET resection. ** Excluding one 10 mm residual scar post non-curative endoscopic rectal NET resection.

A flowchart of the patients and lesions is presented in Figure 1. ESD failed in three patients who underwent curative surgical therapy in the same hospital admission: a large 100 mm ascending colon adenoma and two colon adenocarcinomas exhibiting a "muscle retracting sign". One R0-resected 30 mm ascending colon adenoma harbored a 4/7 mm submucosal poorly differentiated (G3) NET (mixed adenoneuroendocrine carcinoma).

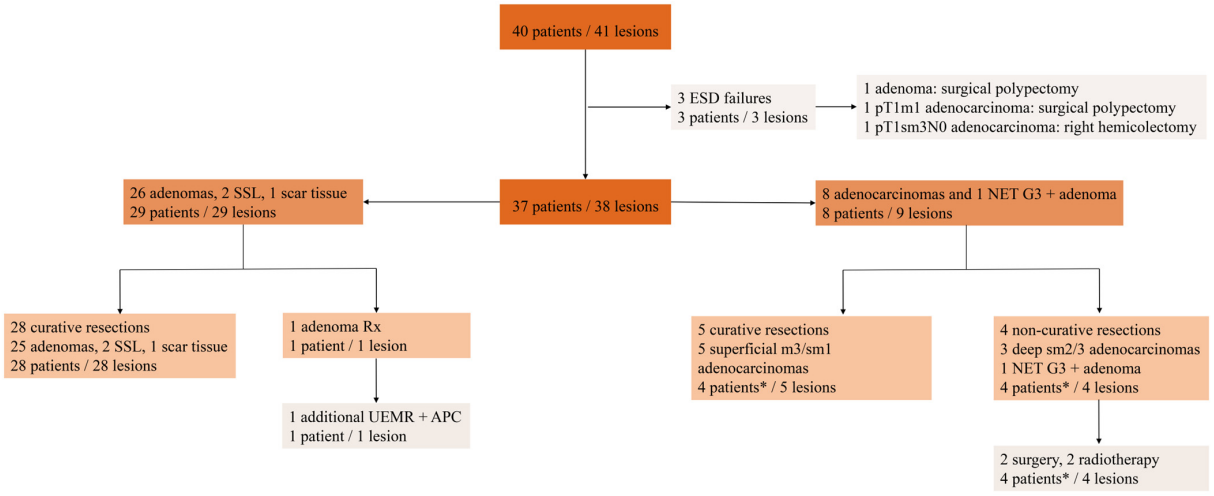

Figure 1. Flowchart of the patients and lesions. * One patient had two lesions.

The ESD results are presented in Table 2. There was one intraprocedural perforation for a curatively resected rectal T1m3 adenocarcinoma exhibiting a "muscle retracting sign", successfully managed conservatively by clip closure, antibiotics and surveillance. * One patient had two lesions, one rectal superficial sm1 adenocarcinoma with curative resection and another lower rectal deep sm3 adenocarcinoma for with non-curative resection for which underwent radiotherapy.

Table 2. ESD results.

ESD Efficacy	
- Success	38 of 41 procedures (92.7%)
- Technique	36 of 38 (94.7%) ESD/2 of 38 (5.3%) hybrid ESD *
- En bloc/piecemeal	37 of 38 (97.4%) en bloc/1 of 38 (2.6%) piecemeal **
- R0 resection	35 of 38 lesions (92.1%) ***
- Curative resection	33 of 38 lesions (86.8%)
ESD complications	
- Perforation	1 of 38 (2.6%)
- Delayed bleeding	3 of 38 (7.9%)

* A 20 mm ascending colon adenoma and a 30 mm descending colon T1sm1 adenocarcinoma. ** A 15 mm adenoma contiguous to an ileo-rectal anastomosis. *** One Rx lateral adenoma and 2 deep R1 sm3 adenocarcinomas.

At the end of the procedure, the wall defect was closed completely with metallic clips in 14 lesions (36.8%) and PuraStat was applied onto the resection bed in 18 lesions (47.4%), while the remaining 6 lesions had their post ESD wall defect untreated.

Clip closure was used more frequently in colonic lesions (12 of 16 colonic lesions vs. 2 of 22 rectal lesions, $p < 0.001$). Its use was not dependent on lesion diameter (clip closure 30 mm [20–60] vs. 37.5 mm [10–150], $p = 0.482$) and on the presence of anticoagulant therapy (clip closure in 2 of 8 patients with anticoagulant vs. 12 of 30 patients without, $p = 0.684$).

PuraStat was significantly more frequently applied in rectal lesions (16 of 22 rectal lesions vs. 2 of 16 colonic lesions, $p < 0.001$). It was also used in larger lesions (40 mm [10–150] vs. 30 mm [20–60], $p = 0.167$, not significant) and in patients with anticoagulant therapy (6 of 8 patients with anticoagulants vs. 12 of 30 patients without, $p = 0.117$, not significant).

The six lesions without clip closure or PuraStat application were smaller (median diameter 25 mm) [20–50] rectosigmoid lesions in patients without anticoagulants.

There were three patients who experienced CSDB after ESD for rectal lesions; their details are presented in Table 3. The univariate analysis for CSDB is presented in Table 4.

Table 3. Patients with delayed bleeding. Y—yes, N—no; NOAC—non-vitamin K oral anticoagulant; G2—grading 2, moderate differentiation; Sm1—superficial submucosal layer involvement.

	Patient 1	**Patient 2**	**Patient 3**
Sex (M/F)	M	F	M
Age (years)	68	55	47
Hypertension	Y	N	N
Anticoagulants	Y, NOAC, resumed	N	N
Lesion diameter (mm)	12	15	40
Lesion location	Rectal	Rectal	Rectal
Dentate line	Y	N	N
Residual post-surgery	Y	N	N
Perianastomotic	N	Y	N

Table 3. *Cont.*

	Patient 1	**Patient 2**	**Patient 3**
Histology	Adenoma	Adenoma	Adenocarcinoma, G2, sm1, R0
Clip closure	N	N	N
PuraStat	Y	Y	Y
Time to delayed bleeding	9 days	36 h	24 h
Prolongation of hospitalization	N	Y	Y
Readmission	Y	N	N
New endoscopic evaluation	Y	Y	Y
Endoscopic hemostasis	Y	Y	Y

Table 4. Univariate analysis of clinically significant delayed bleeding predictive factors.

		Delayed Bleeding	**No Delayed Bleeding**	**Univariate Analysis**
Diameter (mm)		15 (12–40)	35 (10–150)	$p = 0.136$
Age (years)		56.7 ± 10.6	64.2 ± 10.7	$p = 0.250$
Anticoagulants	Yes	1	7	$p = 0.519$
	No	2	28	
Location	Rectum	3	19	$p = 0.249$
	Colon	0	16	
Clip closure	Yes	0	14	$p = 0.283$
	No	3	21	
PuraStat	Yes	3	15	$p = 0.097$
	No	0	20	

4. Discussion

We found a higher CSDB incidence of 7.9% (3 events out of 38 cases, 95% CI [1.7–21.4%]) versus 2.8–4.3% as reported by the ESGE ESD technical guidelines [2]. Other authors have also found similar higher incidences of delayed bleeding of 4.1 to 17.5% [10]. We included only three patients with CSDB for whom endoscopic evaluation with hemostasis by thermocoagulation was necessary. Despite thoroughly washing any traces of blood from the colorectal lumen at the end of the procedure, three other patients with ESD for rectosigmoid lesions exhibited some minute quantity of diluted blood per rectum at 24 h, which stopped spontaneously. These were not considered CSDB and were not included in the analysis.

The risk factors for CSDB after ESD were included in the following predictive scores: the Korean risk score (rectosigmoid location, lesion diameter > 30 mm, use of antiaggregants) and the Limoges score (rectal location, lesion diameter > 50 mm, antiaggregants/anticoagulants, age > 75, and an American Society of Anesthesiology (ASA) risk score of III or IV) [10,11]. In our series, no predictive risk factors for CSDB were found in the univariate analysis (Table 4). Multivariate analysis by binary logistic regression was not performed as the number of events was small [12]. However, all CSDB cases occurred after ESD for rectal lesions, but the association did not reach statistical significance.

A meta-analysis of prophylactic clip closure after colorectal ESD (three randomized controlled trials (RCT), two propensity-score-matched trials and five retrospective studies) found a significantly reduced risk for delayed bleeding (17 events of 939 ESDs with clip

closure vs. 69 events of 1074 ESDs without clip closure, odds ratio = 0.3, 95% CI [0.17–0.52]) [3]. But the effect was not valid for the three randomized controlled trials included (two events of 194 ESDs with clip closure vs. five events of 207 ESDs without clip closure, odds ratio = 0.43, 95% CI [0.08–2.28]). In our series, clip closure was mostly used for colonic lesions and was not protective for CSDB after ESD. Even though statistical significance was not attained, the protective effect may be clinically meaningful, and further validation is necessary (0 events in 14 cases with clips versus 3 events in 24 cases without clips, $p = 0.283$). Note that clip closure was not protective for CSDB in the large prospective cohort of colorectal ESD lesions, validating the Limoges bleeding score (odds ratio = 1.59, 95% CI [0.73–4.18], $p = 0.26$) [10].

There are four prospective publications on PuraStat application for hemostasis and delayed bleeding prevention after colorectal ESD (three observational non-comparative trials and one RCT) [13–16]. One team of authors published three of the four publications [14–16], two of three reporting ESD and EMR cases without differentiating them (5 patients and 31 patients, respectively, no delayed bleeding) [14,15]. There were only 2 events, 1 in an observational study (one event in 15 ESDs) [13] and the other in a comparative study, measured as a secondary objective (one event in 18 ESDs with PuraStat application vs. one event in 25 ESDs without PuraStat application) [16]. In total, there were two instances of delayed bleeding in fewer than 69 ESDs with PuraStat application (this number included colorectal EMRs). In our study, PuraStat application was significantly more frequently applied for rectal lesions and was non-significantly more frequent after ESD for larger lesions and in patients with anticoagulant therapy. This may explain the fact that not only was PuraStat not protective for delayed bleeding in the univariate analysis, but all events occurred in patients with PuraStat application (three events in 18 ESDs with PuraStat application vs. no events in 20 ESDs without PuraStat application, $p = 0.097$). As stated, multivariate analysis could not help to define independent CSDB predictive factors.

Note that few patients for whom colorectal EMR and PuraStat have been used for delayed bleeding prevention are reported to date. One series reported two instances of delayed bleeding in 17 patients (11.8% bleeding rate) [17]. The two delayed bleeding cases were in the rectum, had a 50 mm diameter and were piecemeal EMRs.

The limitations of this paper are the small number of events and the selection bias for the prophylactic method (clip closure, PuraStat application). Nevertheless, the three events of our paper add real-world data to the existing two instances of delayed bleeding in patients with colorectal ESD and PuraStat application reported to date, with a total of five events in up to 107 colorectal ESDs. A future individual-participant-data meta-analysis based on these data may be foreseen.

The limited data do not yet support the efficacy of PuraStat for delayed bleeding prevention after colorectal ESD. A randomized trial with delayed bleeding prevention as the main objective for PuraStat application after colorectal ESD is warranted.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: All research data can be found in the Clinical Trials registry "Endoscopic Submucosal Dissection Registry (ESDREG)" (ClinicalTrials.gov identifier: NCT06033976).

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