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ORIGINAL ARTICLE

Risk Factors, Clinical Course, and Management of Delayed Perforation After Colorectal Endoscopic Submucosal Dissection: A Large-Scale Multicenter Study

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Abstract

Introduction Delayed perforation (DP) remains a significant complication of colorectal endoscopic submucosal dissection (ESD). This study analyzed the risk factors, clinical course, and management for DP following colorectal ESD.

Methods We retrospectively reviewed 4,632 consecutive colorectal ESD cases from 13 institutions between January 2006 and May 2024. DP cases were identified, and the incidence rate, along with patient/lesion characteristics (as tumor size, location, and severe fibrosis) were assessed. The clinical course, including onset timing, initial treatments, need for surgery, and risk factors were examined.

Results DP occurred in 18 cases, with an incidence rate of 0.39% [95% confidence interval (CI): 0.24–0.62]. The mean tumor size was 49.7 ± 35.7 mm. The rates of right-sided colon lesions and severe fibrosis were observed in 77.8 and 61.2%, respectively. DP occurred on post-procedure day 1 in 55.8% of cases, day 2 in 22.2%, and on day 3 or later in 22.2%. Initial DP management included conservative treatment in five cases (27.8%), endoscopic closure in six (33.3%), and surgery in seven cases (38.9%). Among the six cases managed endoscopically, five (83.3%) were successfully managed without surgery. Finally, surgery was required in 11 cases (61.1%). Multivariate analysis (odds ratio [95%CI]) identified severe fibrosis (4.61 [1.50–14.20], p = 0.007), and long procedure time (1.01 [1.00–1.02], p = 0.042), as significant risk factors for DP, while complete closure was inversely correlated with DP risk (0.12 [0.01–0.96], p = 0.046).

Conclusions This study identified DP incidence and risk factors after colorectal ESD, with some cases requiring surgery. Endoscopic treatment may prevent surgery.

Keywords Delayed perforation · Endoscopic submucosal dissection · Colorectum · Endoscopic closure · Clipping

Introduction

Colorectal endoscopic submucosal dissection (ESD) is spreading worldwide, enabling en-bloc resection of large lesions [1–3]. To overcome challenges such as severe fibrosis and poor operability, various devices and techniques, including traction devices and the pocket-creation method, have been developed [4–7]. Despite these advancements, delayed perforation (DP) remains a significant complication of colorectal ESD [1–3, 8, 9]. A meta-analysis reported the incidence of DP after colorectal ESD to be 0.22% (95% confidence interval [CI]: 0.11–0.46) among 3,887 patients across 30 studies [10].

The standard management of DP typically involves urgent surgery to prevent fecal and bacterial leakage from the colon [8, 9]. In a Japanese retrospective study of colorectal ESD cases, among 9 cases of DP, 56% were treated surgically while 44% were managed conservatively with fasting and antibiotics [11]. With advancements in endoscopic tools, such as improved clip technology, carbon dioxide insufflation, and novel techniques, the efficacy of endoscopic closure has improved significantly [12]. Recent reports have highlighted the successful endoscopic management of DP following colorectal ESD without the need for surgery, utilizing specialized devices [10, 13–16].

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However, no large-scale studies have comprehensively examined the clinical course and treatment strategies, particularly the role of endoscopic closure in DP management. In this study, we aimed to analyze the detailed clinical course and identify the risk factors associated with DP following colorectal ESD in a large multicenter cohort. We also tried to determine the surgical or non-surgical treatment following DP and the outcomes.

Methods

We retrospectively analyzed 4,632 consecutive colorectal ESD cases performed at 13 affiliated institutions between January 2006 and May 2024, identifying cases of DP. Following the guidelines of the Japan Gastroenterological Endoscopy Society (JGES), colorectal ESD was indicated for endoscopically diagnosed early neoplastic lesions measuring ≥ 20 mm [1]. Endoscopic diagnosis was performed using narrow-band imaging (NBI), blue laser/light imaging (BLI), and pit pattern observation [17, 18]. Exclusion criteria included familial adenomatous polyposis, systemic infection, and performance status of ≥ 3. Regarding the management of DP, surgery was considered the standard treatment. However, patients with mild abdominal pain, low inflammatory markers, and minimal leakage on computed tomography (CT), were treated conservatively. Endoscopic closure for DP was introduced after 2022, following evidence from multiple studies published in 2020 demonstrating its efficacy in preventing urgent surgery [13, 15, 19]. Endoscopic closure was considered for cases with localized peritonitis on CT and stable clinical conditions. The decision to perform endoscopic closure was made at the discretion of the treating endoscopist based on the specific circumstances of each case.

Study Endpoints

In Analysis 1, the DP incidence was calculated with a 95% CI (Fig. 1). The DP incidence before 2021 and after 2022 were also analyzed. Patient and lesion characteristics in DP cases, such as age, sex, medications (anticoagulants, antiplatelets, steroids), hemodialysis status, lesion location, size, and morphology were analyzed. Therapeutic outcomes of ESD in cases with DP as operator experience, severe fibrosis, intra-procedural severe bleeding, intra-procedural perforation, type of main knife used, ESD procedure time, en bloc resection, R0 resection, histopathological diagnosis, endoscopic closure after ESD, and delayed bleeding were also analyzed. The clinical course of DP as the onset timing, severity of abdominal pain, need for surgery, hospital stay post-ESD, initial treatments (conservative therapy, endoscopic closure, surgery), success rates of preventing surgery for each treatment, peak white blood cell (WBC), C-reactive protein (CRP), and total hospital stay were analyzed. Initial treatments before 2021 and after 2022 were also examined.

In Analysis 2, the risk factors of DP were assessed, comparing cases with DP to cases without DP. The effect of complete closure after ESD in cases with DP was also examined, compared to cases without DP since 2020. Cases requiring surgery due to DP were compared to those managed without surgery. Additionally, the conversion to surgery after conservative treatment and endoscopic closure were

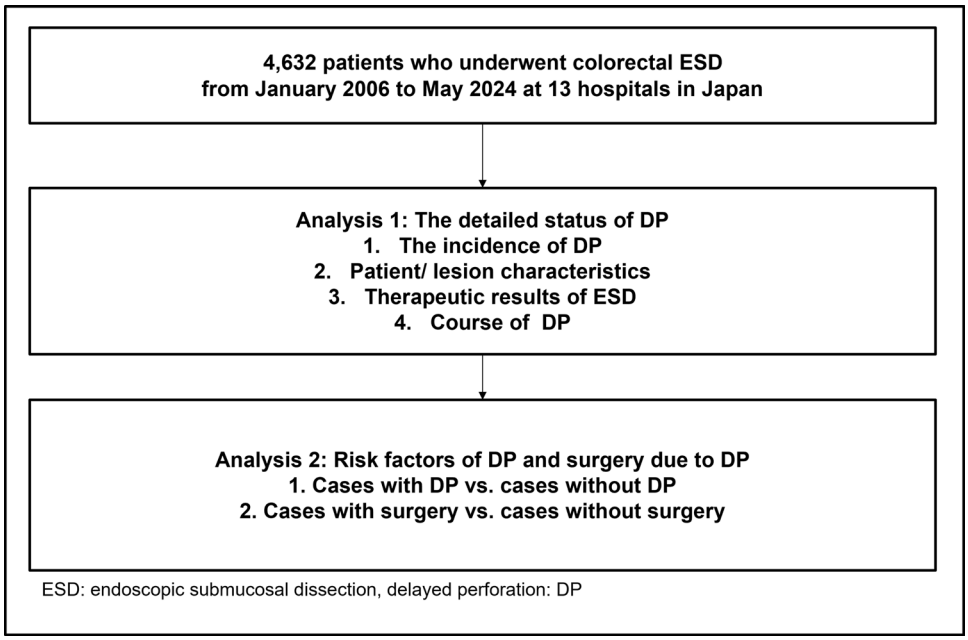

Fig. 1 Study flow

examined. A literature review was also performed to summarize reported cases of endoscopic closure for DP.

Definitions

For antithrombotic drugs, aspirin, thienopyridines, and cilostazol were classified as antiplatelets, while warfarin and direct oral anticoagulants were classified as anticoagulants. The timing for discontinuation and resumption of these drugs was generally based on the guidelines of the JGES [20]. Operators were defined as "experts" if they had performed at least 100 colorectal ESD procedures. Lesion locations were divided into three regions: right-sided colon (cecum to transverse colon), left-sided colon (descending colon to sigmoid colon), and rectum. Lesion size was calculated based on the resected specimen. Lesions were morphologically classified as non-polypoid or polypoid, according to the Paris classification [21].

Severe fibrosis was defined as the presence of a whitish, muscle-like structure in the submucosal layer during ESD [22]. Intraprocedural severe bleeding was defined as bleeding that required the use of hemostatic forceps for control during the ESD procedure. Complete closure was defined when the defect's surface was no longer visible after clipping [23]. DP was defined as the presence of free air within 14 days post-ESD detected by CT unrelated to intra-procedural perforation with either severe abdominal pain with rebound tenderness or high inflammation level of blood examination. The status of abdominal pain was classified as follows: severe pain required opioid analgesics, while minor pain either required no medication or was managed with non-opioid analgesics. Histopathological diagnosis was performed according to the World Health Organization classification [24]. R0 resection was defined as resection with histopathologically negative horizontal and vertical margins.

ESD Procedure and Endoscopic Closure

The ESD technique was performed following a previous report [7]. In brief, after the injection of hyaluronic acid (MucoUp, Boston Scientific Japan, Tokyo, Japan) or sodium alginate (Liftal K, Kaigen Pharma, Osaka, Japan), an ESD knife such as a needle-type knife or scissor-type knife was used for a mucosal incision from either the oral or anal side of the lesion. Submucosal dissection was performed using either a traction device or the pocket-creation method. Finally, en-bloc resection was achieved, followed by partial/complete closure of the ESD defect at the operator's discretion using clips in cases where there was potential for extensive muscular injury or a high risk of delayed bleeding. Blood tests, including WBC counts and CRP levels, were conducted 1 and 2 days post-ESD. Diet was typically resumed on the second day after the procedure, and patients were discharged 3–5 days following ESD. Endoscopic closure was performed using standard clips (ST-C) with or without reopenable function, over-the-scope clip (Ovesco Endoscopy GmbH, Tüebingen, Germany), the MANTIS Closure Device (MCD; Boston Scientific Co., MA, USA), and the SureClip Traction Band (SCTB; Micro-Tech, Nanjing, China) according to previous papers [12, 14, 25].

Statistical Analyses

The Mann–Whitney U test or chi-squared test was used for statistical analysis. Multivariate analysis was performed using the Cox proportional hazards model and age, sex, and variables with $p < 0.05$ in the univariate analysis were included. When many candidate factors were detected, selective factors were examined in the model to keep statistical quality. Before conducting the multivariate analysis, variables exhibiting high multicollinearity were excluded. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using statistical software (SPSS software, version 22.0; IBM Japan Ltd., Tokyo, Japan or R version 4.2.2 for Windows, R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 4,632 colorectal ESD cases, DP occurred in 18 cases (0.39%, 95% CI: 0.24–0.62) (Table 1). The incidence before 2021 and after 2022 were 0.28% (9/3,223) and 0.64% (9/1,409) ($p = 0.07$). The right-sided colon was the location in 77.8% of cases. Two cases of intraprocedural perforation developed a new perforation site after ESD as DP, which was identified through urgent endoscopy for closure and surgery.

Regarding, the timing of DP, 11.4% occurred on the day of ESD and 44.4% on post-procedure day 1 (Table 2, Supplemental Table 1). Ultimately, 11 of the 18 cases (61.1%) required surgery. Among the 11 cases, 3 required artificial anus. Initial treatment included conservative management in five cases, endoscopic closure in six cases, and surgery in seven cases (Fig. 2). All patients treated with conservative management or endoscopic closure received antibiotics and were kept fasting. The rates of conservative treatment /endoscopic closure/surgery for initial treatment before 2021 and after 2022 were 33.3%(3)/0.0%(0)/66.7%(6) and 22.2%(2)/66.7%(6)/11.1%(1) ($p < 0.01$). Endoscopic closure was successful in five of the six cases (83.3%).

After the exclusion of cases, univariate analysis comparing cases with and without DP revealed significant differences in lesion size ($p < 0.01$), severe fibrosis ($p < 0.01$), ESD procedure time ($p < 0.01$), and complete closure after ESD ($p = 0.01$) (Table 3). Multivariate analysis (odds ratio [95%CI]) identified severe fibrosis (4.61 [1.50–14.20],

Table 1 Patient/lesion characteristics and therapeutic results of ESD about cases with DP in colorectal ESD

Lesion number of DP	18
DP incidence, overall, n (%) [95%CI]	0.39 [0.24–0.62]
DP incidence, before 2021/after 2022, n (%)	9/9 (0.03/0.06)
Age, mean ± SD (range)	66.5 ± 10.5 (50–86)
Sex, % (n) male/female	72.2/27.8 (13/5)
Medications, anticoagulant/antiplatelet/steroid, n (%)	0/1/2 (0/5.5/11.1)
Hemodialysis, n (%)	0 (0.0)
Locations, C/A/T/D/S/R, n (%)	5/5/4/1/2/1 (27.8/27.8/22.2/5.6/11.1/5.6)
Size, mean ± SD, mm (range)	49.7 ± 35.7 (15–140)
Morphology, P/NP, n (%)	6/12 (33.3/66.7)
Operators of ESD, experts/non-experts, n (%)	16/2 (88.9/11.1)
Severe fibrosis, n (%)	11 (61.2)
Use of traction device, n (%)	5 (27.8)
Intraprocedural severe bleeding, n (%)	5 (27.8)
Intraprocedural perforation, n (%)	2 (11.1)
Type of main knife, needle/scissors, n (%)	6/12 (33.3/66.7)
ESD procedural time, mean ± SD, min (range)	154 ± 141 (30–570)
En bloc resection, n (%)	17 (94.4)
R0 resection, n (%)	15 (83.3)
Histopathological diagnosis, SSL + Ade/T1a/T1b, n (%)	13/3/2 (43.8/25.0/18.8/12.5)
Endoscopic closure after ESD, full/partial/none, n (%)	1/8/9 (5.6/44.4/50.0)
Delayed bleeding, n (%)	0 (0.0)

DP delayed perforation, *ESD* endoscopic submucosal dissection, *SD* standard deviation, *CI* confidence interval, *P* polypoid, *NP* non-polypoid, *C* cecum, *A* ascending colon, *T* transverse colon, *D* descending colon, *S* sigmoid colon, *R* rectum, *SSL* sessile serrated lesions, *Ade* adenoma

Table 2 The clinical course of cases with DP in colorectal ESD

Case number	18
Onset of delayed perforation, n (%)	2/8/4/4
ESD day/post 1 days/post 2 days/post 3 ≤ days	(11.1/44.4/22.2/22.2)
Abdominal pain, nothing/minor/severe, n (%)	0/4/14 (0.0/22.2/77.8)
Rate of surgery, % (n)	61.1 (11)
Initial treatment, conservative/endoscopic closure/surgery, n (%)	5/6/7 (27.7/33.3/38.9)
WBC (peak), ul, mean ± SD (range)	14,832 ± 5,064 (5200–27680)
CRP (peak), mg/dl, mean ± SD (range)	18.3 ± 7.5 (10.0–38.1)
Hospital stay, day, mean ± SD (range)	18.2 ± 11.1 (6.0–39.0)
Hospital stay according to initial treatment, conservative/endoscopic closure/surgery, day, mean ± SD	16.8 ± 10.8/13.0 ± 10.8/23.7 ± 10.6*

* There was no significant difference between endoscopic closure and surgery ($p = 0.05$)

DP delayed perforation, *ESD* endoscopic submucosal dissection, *CI* confidence interval, *SD* standard deviation, *WBC* white blood cell, *CRP* C-reactive protein

p = 0.007), long ESD procedure time (1.01 [1.00–1.02], p = 0.042), and complete closure (0.12 [0.01–0.96], p = 0.046, inversely correlated) as significant factors for DP.

When comparing cases that required surgery to those that did not, significant differences were observed in the rate of cecal location (p = 0.01) and hospital stay duration (p < 0.01) (Table 4). We also compared the conversion-to-surgery group (n = 4) with the successful non-surgical treatment group (n = 7) (Supplemental Table 2). Significant differences were observed in lesion location, WBC, and hospital stay.

A literature review, including our six cases, identified 12 reported cases of endoscopic closure for DP (Table 5) [13–16, 19, 26]. Among these, 10 cases (83.3%) occurred in the right-sided colon. Three cases were managed using ST-C, while nine required specialized devices or techniques, including a polyglycolic acid sheet, an endoloop

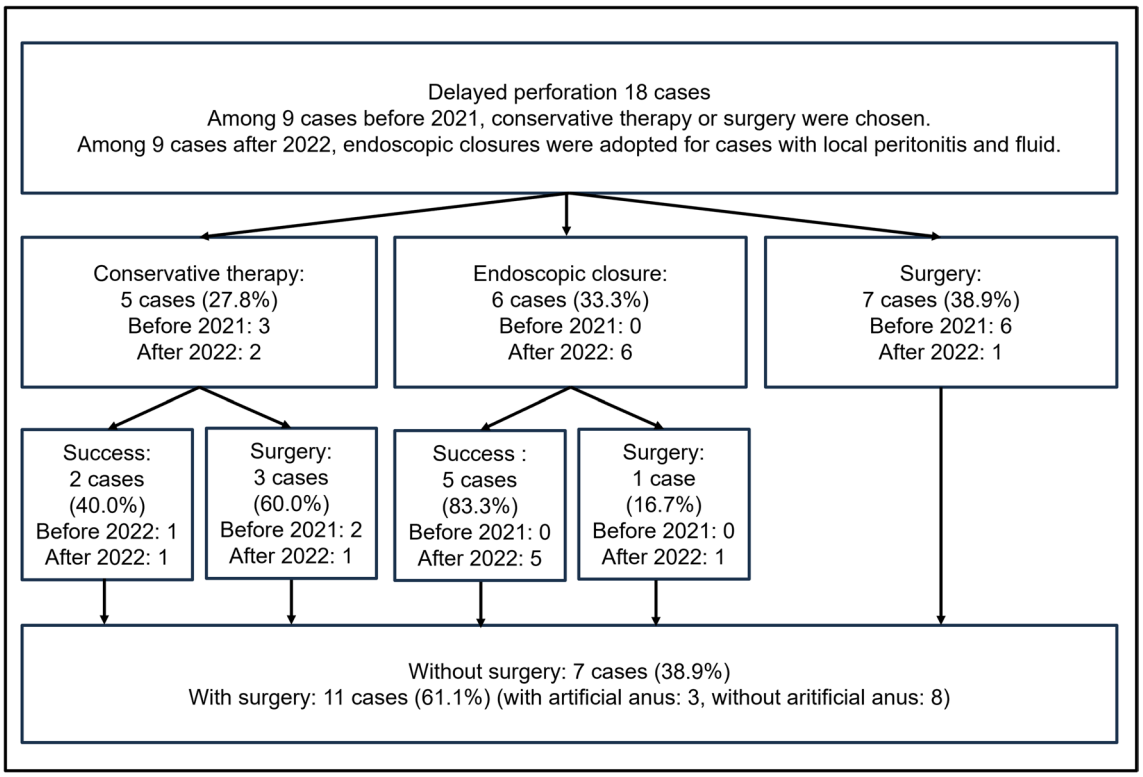

Fig. 2 The clinical course of cases with DP in colorectal ESD

Table 3 Risk factors of DP in colorectal ESD

	Univariate analysis		p value	Multivariate analysis		p value
	With DP	WIthout DP		OR	95%CI	
Lesion number	18	1871				
Age, mean ± SD	66.5 ± 10.5	68.2 ± 11.0	0.32			
Sex, % (n) M/F	13/5 (72.2/27.8)	1030/841 (55.1/44.9)	0.14			
Location, right-sided, n (%)	14 (77.8)	996 (53.6)	0.06	2.26	0.67–7.59	0.189
Size, mean ± SD, mm (range)	49.7 ± 35.7 (15–140)	31.4 ± 15.2	< 0.01	1.01	1.00–1.01	0.480
Morphology, % (n) Po/Non-po	6/12 (33.3/66.7)	340/1531 (18.2/81.8)	0.09	n.c		
Severe fibrosis, n (%)	11 (61.2)	272 (14.5)	< 0.01	4.61	1.50–14.20	0.007
Intraprocedural perforation, n (%)	2 (11.1)	38 (2.0)	0.06	n.c		
ESD procedural time, mean ± SD, min	154 ± 141 (30–570)	71.3 ± 49.8	< 0.01	1.01	1.00–1.02	0.042
En bloc resection, % (n)	17 (94.4)	1798 (96.1)	0.80	n.c		
Complete closure after ESD, % (n)	1 (5.6)	257 (35.8%)*	0.01	0.12	0.01–0.95	0.045

DP delayed perforation, *ESD* endoscopic submucosal dissection, *M* male, *F* female, *OR* odds ratio, *Cl* confidence interval, *SD* standard deviation, *n.c.* not calculated, *right-sided* cecum to transverse colon, *Po* polypoid, *Non-po* non-polypoid

*This value was only examined in only 718 ESD cases after 2020

(Olympus Medical Co., Tokyo, Japan), an OTSC, MCD, and SCTB (Fig. 3). In one case managed with OTSC, perforation was initially closed, but DP recurred the following day, necessitating urgent surgery. All six cases in our study underwent a CT re-examination 1–3 days post-procedure

Table 4 The comparison of surgery group vs. non-surgery group due to DP in colorectal ESD

	With surgery	Without surgery	p value
Case number	11	7	–
Age, mean ± SD (range)	66.5 ± 10.2	66.8 ± 11.6	0.95
Sex, % (n) male/female	8/3 (72.7/27.3)	5/2 (71.4/28.6)	0.95
Lesion size	48.0 ± 39,4	44.7 ± 32.0	0.85
Lesion location C/A/T/D/S/R, n (%)	5/3/1/0/2/0 (45.5/27.3/9.1/0/18.2/0)	0/2/3/1/0/1 (0/28.6/42.9/14.3/0.0/14.3	0.08
Lesion location C, n (%)	5 (45.5)	0 (0.0)	0.01
Sever fibrosis, n (%)	8 (72.7)	3 (42.9)	0.44
ESD procedure time, mean ± SD	186.0 ± 153.0	103.8 ± 118.5	0.24
Parian and complete closure after ESD, % (n)	3 (27.2)	6 (85.7)	0.05
WBC (peak), ul, mean ± SD (range)	15,667 ± 5904 (5200–27,680)	13,521 ± 3359 (9300–20,000)	0.19
CRP (peak), mg/dl, mean ± SD (range)	19.8 ± 8.9 (10–38.1)	15.9 ± 4.3 (10.0–22.0)	0.15
Hospital stay, day, mean ± SD (range)	24.2 ± 10.3 (10–39)	8.7 ± 1.7 (6–11)	< 0.01

DP delayed perforation, *ESD* endoscopic submucosal dissection, *SD* standard deviation, *M* male, *F* female, *C* cecum, *A* ascending colon, *T* transverse colon, *D* descending colon, *S* sigmoid colon, *R* rectum, *WBC* white blood cell, *CRP* C-reactive protein

to assess the amount of air and liquid before resuming an oral diet, to evaluate its success.

Discussion

In this study, which analyzed the largest cohort of colorectal ESD cases (n = 4632), the incidence of DP was 0.39% (95% CI: 0.24–0.62). A meta-analysis reported an overall DP rate of 0.22% (95% CI: 0.11–0.46), with a lower rate of 0.18% (95% CI: 0.08–0.42) in 25 Asian studies and a higher rate of 1.2% (95% CI: 0.29–4.6) in five Western studies [10]. Additionally, a multicenter study in Korea found a DP rate of 0.1% (3/2,046), while a Japanese study reported a rate of 0.4% (4/1,111) [27, 28]. This variability in DP rates may be influenced by factors such as geographic region, institutional practices, endoscopist experience, and specific indications for ESD.

Several reports have identified potential risk factors of DP, although most lacked statistical validation. For instance, one study analyzing nine DP cases found significantly higher median peak WBC and CRP levels (13,400/μl and 12.9 mg/dl) in patients with DP compared to those without (7700/ul and 0.4 mg/dl) [11]. Moreover, a higher prevalence of right-sided colon lesions was noted in cases with DP (67%) compared to those without (55%), suggesting that right-sided location may be a risk factor [9, 19]. Other identified risk factors included larger tumor size and the presence of severe fibrosis [9, 29]. Our multivariate analysis confirmed severe fibrosis, and long ESD procedure time as significant risk factors for DP, while complete closure was inversely correlated with DP risk. Contrary to previous reports, the right-sided colon was not a significant factor; however, a cecal location was identified as a significant risk factor for surgical intervention in DP. We also considered that excessive coagulation of the muscular layer contributed to DP, particularly in cases with severe fibrosis. In the right-sided colon, limited scope maneuverability and a thinner colonic wall compared to the rectum may have increased the risk of excessive coagulation during ESD. The rate of DP after 2022 was higher compared to that before 2021. This was also probably due to excessive coagulation and severe fibrosis. We adopted the VIO3 electrosurgical unit, which has been introduced since 2022 and has higher electrical power than the previous models. Additionally, due to improvements in dissection strategies, devices, and closure techniques, we performed cases with diffuse severe fibrosis that were not treated with ESD before 2022. We were also able to demonstrate the effectiveness of complete clip closure in preventing DP, whereas previous studies could not confirm its efficacy due to the small number of DP cases. Moreover, in DP cases requiring surgery, hospital stays were significantly longer. Thus, DP should be prevented. To our knowledge, this is the first study detailing DP cases, including surgical cases, and related factors.

We summarized cases of DP managed with endoscopic closure. The adoption of endoscopic closure in 2022 significantly changed the initial treatment approach for DP compared to the period before 2021. The decision to proceed with endoscopic closure should be made cautiously, considering factors such as fluid accumulation identified via CT, endoscopist experience, perforation size, and the availability

Table 5 Details of 12 cases with endoscopic closure for DP after colorectal ESD in the literature review including our cases

Ref, reported year	No	Age	Sex	Location	Size, mm	Mor	Onset of DP (day)	WBC (peak)/μl	CRP (peak) mg/dl	Way of closure	Style of closure	Surgery	HS (day)
Xiao et al. [26]	2	49	F	S	-	NP	2	12,300	NR	OT EP	P	N	29
Xiao et al. [26]	3	77	M	A	-	NP	2	14,500	NR	OT	F	N	12
Nagami et al. [13]	1	81	M	A	40	NP	2	NR	NR	PGA	P	N	16
Kuwabara et al. [16]	6	68	F	T	20	NP	2	NR	NR	OTSC	P	N	12
Zhou et al. [19]	4	54	M	T	30	NP	1	NR	NR	ST-C	F	N	4
Tsukida et a. [15]	5	47	M	T	60	P	2	NR	NR	RSM	F	N	7
Ours	7	75	M	T	25	NP	1	9300	22.1	ST-C	P	N	10
Ours	8	50	M	A	40	P	1	20,000	10.5	ST-C	P	N	6
Ours	9	76	M	A	60	P	3	13,300	12.5	MCD	P	N	9
Ours	10	77	M	C	140	NP	1	22,000	10.2	OTSC	P	Y	35
Ours [14]	11	61	F	T	38	P	1	12,400	19.0	MCD, SCB	F	N	10
Ours	12	70	M	D	20	NP	2	12,390	16.4	SCB	F	N	8

DP delayed perforation, *M* male, *F* female, *A* ascending colon, *S* sigmoid colon, *T* transverse colon, *C* cecum, *D* descending colon, *Mor* morphology, *NP* non-polypoid, *P* polypoid, *WBC* white blood cell, *NR* not reported, *CRP* C-reactive protein, *N* none, *Y* yes, *PGA* polyglycolic acid sheet, *OT* overtube, *ST-C* standard clip, *EP* endoloop, *RSM* ring-string method, *OTSC* over the scope clip, *MCD* MANTIS closure device, *SCB* SureClip traction band, *P* partial, *F* full, *HS* hospital stay

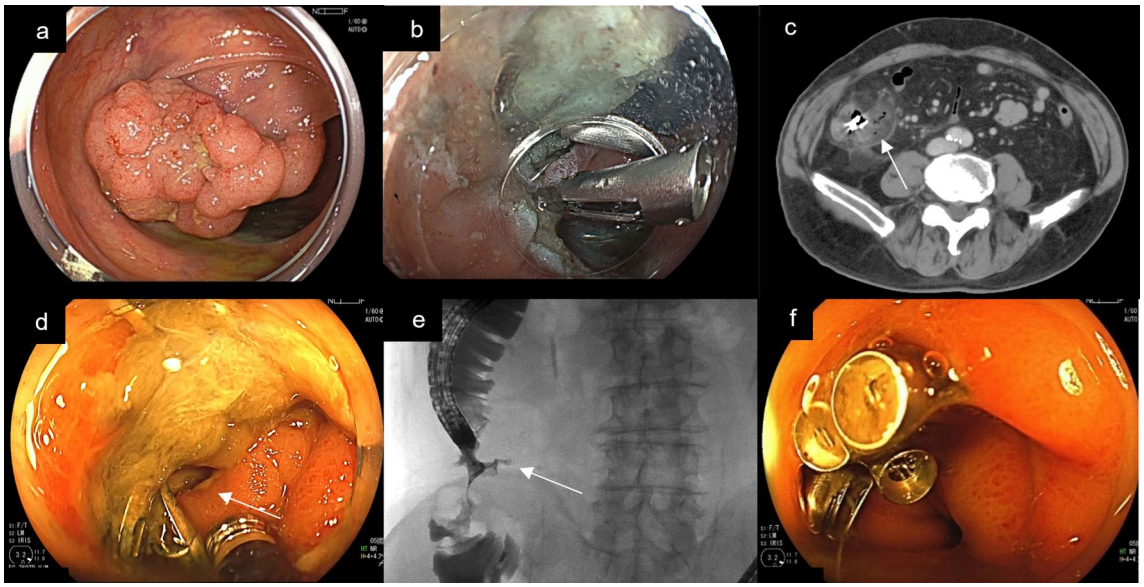

Fig. 3 A case with DP treated by endoscopic closure. **a** A 76-year-old man. A protruding lesion of 40 mm in size on the ascending colon. ESD was performed and severe fibrosis was dissected. **b** The tumor could be resected en-bloc (Total procedure time: 120 min). Endoscopic clipping was performed for the severe fibrosis area after ESD. **c** On postoperative day 1, the patient developed a fever of 38.1 °C without abdominal pain and laboratory tests revealed a WBC of 18,500/μl and a CRP of 2.37 mg/dL. On postoperative day 3, the patient complained minor abdominal pain with mild rebound tenderness and urgent CT showed DP with localized free air and fluid around the ESD site. **d** Urgent colonoscopy detected an ESD ulcer. A partial deep wound at the oral margin of the ulcer (white arrow) was confirmed perforation by contrast medium through the catheter. **e** The leak of contrast medium (iopamidol) was found. **f** The wound and the ulcer were closed with two kinds of clips such as Sure Clips (Micro-Tech, Nanjin, China) and Resolution clip 360 (Boston Scientific Co., MA, USA) due to closure ability and cost. After the endoscopic closure, the leakage was successfully resolved according to the re-examination of CT and the patient's clinical condition improved. He was discharged seven days post-ESD

of suitable devices; however, no standardized guidelines exist for this procedure [1–3, 9, 19]. In addition, several reports emphasized the necessity of consulting surgical teams before attempting endoscopic closure [9, 14, 15]. Successful endoscopic closure requires both an appropriate indication and adequate setup/devices. When determining the indication, consultation with the surgical team and ensuring that the patient is in stable condition with localized peritonitis are essential. In terms of setup/devices, carbon dioxide insufflation is preferred over air because it is absorbed more quickly [30]. In addition, using a waterjet to cleanse the perforation site and fluoroscopy for precise localization of the perforation can improve closure success [14]. Furthermore, having several closing methods and devices readily available is important to ensure the definitive closure of DP.

The nature of DP defects differs from those during ESD, as the base of the defect is often fragile, making standard clips less effective for closure. Therefore, specialized techniques with enhanced closure capabilities are recommended. Tsukida et al. described a handmade traction method [15]. Gweon et al. also showed the usefulness of traction devices in a review [9]. Xiao et al. reported two successful cases of endoscopic closure using a balloon overtube to suction fluid from around the perforation [26]. Nagami et al. utilized polyglycolic acid sheets and fibrin glue along with clips to seal small holes in DP [13]. Kuwabata et al. documented a case successfully closed with an OTSC, known for its strong closure capabilities [16]. In our study, we used two though-the-scope devices: the SCTB and MCD [14, 25, 31]. SCTB has a rubber band with a clip designed originally as a traction device during ESD. However, this device can be used for closure by deploying it to the anal-side mucosa of the defect and then, another clip catches the band and pulls it to the oral-side mucosa at which the clip deployed [14]. Then, additional clips were placed to close the narrowed defect completely. The MCD, featuring a sharp claw, securely grasps the anal-side mucosa and pulls it toward the oral side of the defect [25]. While various suturing devices like Overstitch (Boston Scientific Co., MA, USA) and Stuart (Olympus Co., Tokyo, Japan) are available, their efficacy for DP closure remains undocumented [12, 32]. Furthermore, a unique suturing technique called the reopenable clip-over-the-line method has shown promise for closing large defects post-ESD [33]. However, these devices may require longer procedure times, potentially worsening outcomes in DP cases. Additional investigations are warranted to identify the most suitable devices for endoscopic closure of DP.

This study has inherent limitations, including its retrospective design, which may introduce selection bias. The

treatment decisions for DP were made at the discretion of individual endoscopists, and the control group consisted only of cases with sufficient data for analysis. Complete closure in cases with DP was examined in limited cases after 2020. Muscular injury can be associated with DP. However, its evaluation was difficult in cases of severe fibrosis and we did not include this factor in our study. Furthermore, DP cases presenting with mild abdominal symptoms and moderate inflammation, which should be distinguished from Post-ESD Coagulation Syndrome (PECS), were not detected in this study. Lastly, the number of DP cases was insufficient for a robust multivariate analysis, which may limit the generalizability of our findings.

In conclusion, this study identified DP incidence and risk factors after colorectal ESD. Endoscopic treatment has the potential to prevent surgery in select cases. Complete prophylactic clip closure should be considered for lesions with identified risk factors. Further investigation is required to confirm the efficacy of endoscopic closure to avoid overgeneralizing from the limited sample size.

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Author Contributions NY and RH designed and organized this study. KI, YI, YI, TM, RY, HH, HY, TT, KF, DH, YM, TM, RK, NI, and OD, enrolled patients, collected detailed data, and reviewed the paper. EG supported data analysis and English correlation. YI helped to design this study.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest Yoshida N and Dohi O received a research grant from Fujifilm Co. Yoshida N received lecture fee from Fujifilm. The other authors declare no conflicts of interest.

Ethical approval This study was approved by the ethics committee of Kyoto Prefectural University of Medicine (ERB-C-1704-5, approval data: June 5, 2024) as a partial study of our large-scale retrospective and prospective study and was conducted in accordance with the World Medical Association Declaration of Helsinki. This was a retrospective study and patients' informed consent was obtained with the option opt-out from participating.

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