

Risk Factors for Delayed Bleeding After Endoscopic Resection for Large Colorectal Tumors

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Objective: Endoscopic resection techniques for treating colorectal tumors have advanced recently so that large colorectal tumors can now be treated endoscopically, although some patients experience delayed bleeding after endoscopic resection. Our aim was to clarify the risk factors for delayed bleeding after endoscopic resection for colorectal tumors ≥ 20 mm in diameter. Endoscopic submucosal dissection cases were excluded because of the low incidence of delayed bleeding after such procedures.

Methods: This was a retrospective study using a prospectively completed database and patient medical records at a single, national cancer institution. A total of 403 colorectal endoscopic resections were performed on 375 consecutive patients. We analyzed the database and retrospectively assessed patient age, gender, hypertension and current use of anticoagulant (warfarin) or antiplatelet drugs (e.g. aspirin, ticlopidine) as well as tumor location, size, macroscopic type, histopathological findings, resection method and whether or not placement of prophylactic clips was performed during the endoscopic resection.

Results: The overall rate of delayed bleeding was 4.2% (17/403) and the median interval between endoscopic resection and the onset of delayed bleeding was 2 days (range, 1–14 days). All delayed bleeding cases were successfully controlled by endoscopic hemostasis involving clipping and/or electrocoagulation without the need for surgical interventions or blood transfusions. Based on our univariate analysis, the delayed bleeding rate was significantly higher in both males ($P = 0.04$) and those patients without prophylactic clip placement ($P = 0.04$).

Conclusions: Our study results indicated that prophylactic clip placement may be an effective method for preventing delayed bleeding after endoscopic resection for large colorectal tumors.

Key words: colorectal tumors – endoscopic resection – delayed bleeding

INTRODUCTION

Endoscopic resection (ER) techniques used in the treatment of colorectal tumors have progressed to the point that they have become well established recently because ER is associated with minimal invasiveness and excellent results (1–6). In addition to polypectomy (PO), endoscopic mucosal resection (EMR) and endoscopic piecemeal mucosal resection (EPMR) are now widely accepted in the

treatment of large colorectal tumors and laterally spreading tumors (7–10). There is always a risk of complications with ER, however, despite the best preventative efforts and delayed bleeding, which can occur up to 2 weeks after ER, is one of the more frequent complications (11). Although delayed bleeding is clinically serious, it is difficult to accurately predict the risk of such delayed bleeding (12). The risk of delayed bleeding has been reported to increase as the size

of resected polyps increases (11–15), but there have been no previously published reports that describe the risk factors for delayed bleeding specifically with respect to large colorectal tumors. The aim of the present study was to evaluate and clarify the risk factors for delayed bleeding after ER for colorectal tumors ≥ 20 mm in diameter.

PATIENTS AND METHODS

PATIENTS

ER procedures (PO, *en bloc* EMR and EPMR) were performed on 403 colorectal tumors ≥ 20 mm in diameter in 375 consecutive patients at the National Cancer Center Hospital in Tokyo from January 2003 to December 2006. Patients with inflammatory bowel diseases, thrombocytopenia and non-epithelial neoplasms were excluded from this study as were patients who received an endoscopic submucosal dissection (ESD) because electrocoagulations were usually performed on all visible vessels after the ESD procedure and the rate of delayed bleeding in ESD cases is very low (2%) according to a published report on colorectal ESDs performed in our hospital (16).

We analyzed a prospectively completed database and reviewed patient medical records pertaining to these large colorectal tumors and retrospectively assessed patient age, gender, hypertension and current use of anticoagulant (warfarin) or antiplatelet drugs (e.g. aspirin, ticlopidine) as well as tumor location, size, macroscopic type, histopathological findings, resection method and whether or not placement of prophylactic clips was performed during the ER in an effort to determine the risk factors for delayed bleeding. Delayed bleeding was defined as clinical evidence of bleeding manifested by melena or hematochezia from 0 to 14 days after the procedure that required endoscopic hemostasis. Written informed consent was obtained from all patients before ER in accordance with the Declaration of Helsinki.

INDICATIONS FOR ENDOSCOPIC RESECTION

After observation of a lesion was conducted by conventional endoscopic examination, 0.4% indigo-carmin dye was sprayed over the lesion to enhance its surface detail. High-magnification observation (PCF-240ZI or CF-H260AZI; Olympus Optical Co., Ltd, Tokyo, Japan) with 0.05% crystal-violet stain was then used whenever necessary to evaluate the surface character for pit patterns to differentiate an invasive pattern from a non-invasive pattern. An invasive pattern is characterized by irregular and distorted epithelial crypts observed in a demarcated area, suggesting that submucosal (s.m.) invasion is >1000 μm (17–20). Existence of a non-invasive pattern determined by chromo-magnification colonoscopy was the minimum requirement for all ER candidates.

ENDOSCOPIC PROCEDURES

When anticoagulant and/or antiplatelet drugs were prescribed for non-critical problems, patients were instructed to discontinue the use of such drugs beginning 7 days before their ERs. All ER procedures were performed using an Olympus PCF-Q240ZI or CF-H260AZI video endoscope. PO was performed by snaring without s.m. injection, while the inject and cut technique described in previous reports was used for both EMR and EPMR procedures (1–3,6,8). EPMR was distinguished from EMR whenever a lesion was resected in more than two pieces.

The lesion was first elevated by injecting glycerol into the s.m. layer using a standard 23 G injection needle (Olympus). Glycerol was used as the s.m. injection solution because as we previously reported, a 10% glycerol solution is superior to normal saline for colorectal EMR (21). The lifted lesion was then resected with a round or oval snare in 120 W endocut (effect 3) and 50 W forced coagulation mode (effect 3) using a high-frequency electrical generator (ICC200; ERBE Elektromedizin GmbH, Tübingen, Germany). For purposes of this study, the method of resection was categorized as being either an *en bloc* (PO or EMR) or a piecemeal (EPMR) resection. All resected materials were retrieved for histopathological examination. We subsequently advised all ER patients to refrain from alcohol consumption and heavy exercise for 1 week and to call our hospital immediately if they had any bloody feces.

PROPHYLACTIC CLIP PLACEMENT

We leave the decision on whether clipping is necessary or not after ER to the doctors. When the following situations are a concern, the doctors determine that clipping is necessary: an acute bleeding occurs when a lesion is resected, and blood vessels are suspected to be exposed on the mucosal defect; as tissue coagulation is not sufficient when a lesion is resected, blood vessels are not sufficiently coagulated; a mucosal defect is deep, the muscle layers and serosa are exposed and there is a risk of perforation. Such technique was used solely for the purpose of stopping acute bleeding and not to prevent tumor implantation in those cases in which a lesion was resected in more than five pieces. Approximation of the mucosa at the edge of the post-ER ulcer was performed using hemoclips (HX-600 or HX-610 series; Olympus or Resolution Clip Device; Boston Scientific, Natick, MA, USA) (Fig. 1A–C). When complete closure of a large mucosal defect proved difficult using just hemoclips, clipping of only exposed vessels or complete closure using the endoloop/metallic clip method was performed with a double-channel colonoscope (22).

TUMOR-RELATED FACTORS

The size of each polyp was measured in relation to an open standard PO snare and the macroscopic type was categorized

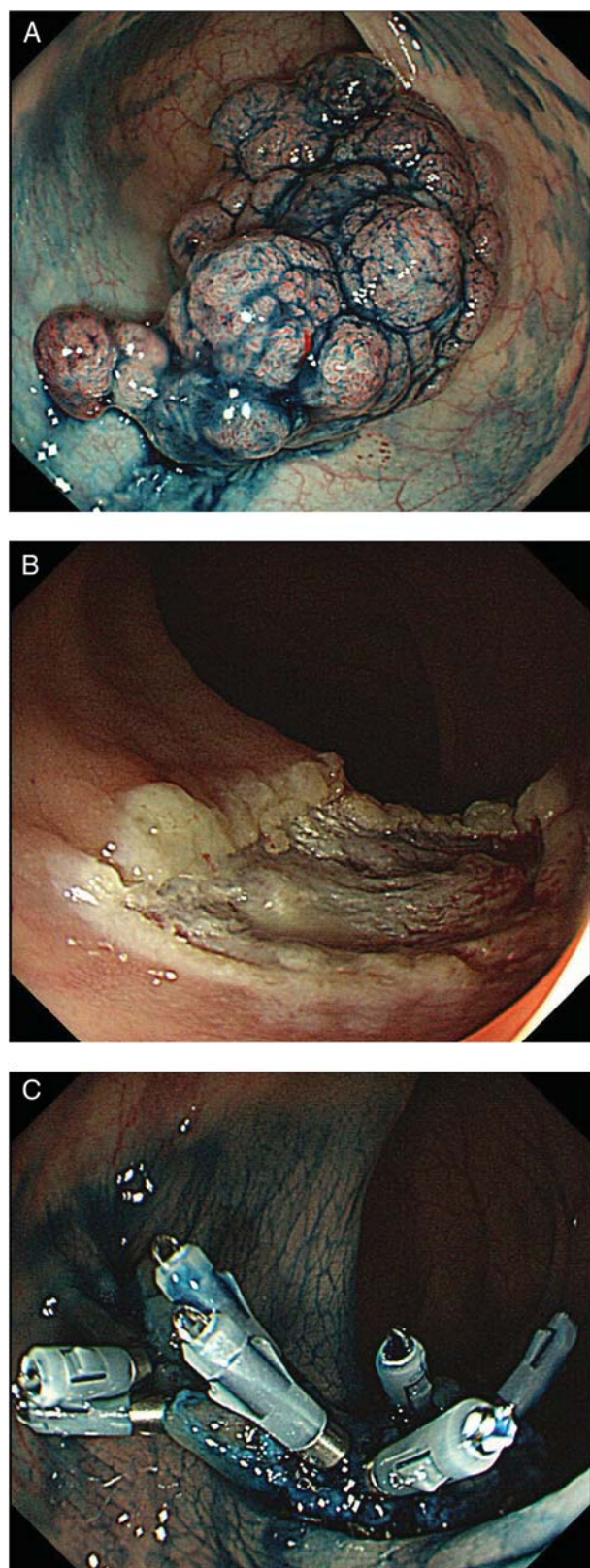


Figure 1. (A) Chromoendoscopic view after indigo-carmin dye spraying showing 50 mm, uneven polypoid lesion (Ip) in the rectum. (B) Endoscopic view after endoscopic mucosal resection showing mucosal defect without any residual tumor. (C) Mucosa at the edge of mucosal defect was approximated using hemoclips thus preventing delayed bleeding.

as being either sessile or other (flat, depressed or recurrent). All specimens were evaluated after being cut into 2 mm slices and examined histopathologically with diagnoses based on the Japanese classification of cancer of the colon and rectum (23) and the Vienna classification (24).

PATIENT-RELATED FACTORS

Patient information was based on a review of available medical records. Hypertension was defined as a patient either having systolic blood pressure of at least 140 mmHg or undergoing antihypertensive therapy. The current use of anticoagulant or antiplatelet drugs was defined as the use of such drugs within 7 days of ER. Only one patient using both anticoagulant and antiplatelet drugs was included in the anti-coagulant group.

STATISTICAL ANALYSIS

Data were reported as mean \pm standard deviation (SD) and median (range) for quantitative variables having normal and skewed distributions, respectively. In comparing baseline characteristics between the two groups of patients with and without delayed bleeding, we used a *t*-test for continuous variables and a Fisher exact test or χ^2 test for dichotomous variables. All statistical analyses were performed using SAS version 8.0 (SAS Institute Inc., Cary, NC, USA) and the *P* value was two-sided with <0.05 used to determine statistical significance.

RESULTS

CLINICOPATHOLOGICAL CHARACTERISTICS

A total of 403 colorectal tumors ≥ 20 mm in diameter were treated by ER in 375 consecutive patients. The mean patient age \pm SD was 63 ± 12 years (range, 22–92 years) and the mean lesion size was 27.1 ± 9.6 mm (range, 20–95 mm).

DELAYED BLEEDING

All delayed bleeding cases are summarized in Table 1. The total number of delayed bleeding cases amounted to 17 lesions (4.2%) in 17 patients (4.5%) and the median interval between ER and the onset of delayed bleeding was 2 days (range, 1–14 days). All delayed bleeding cases were successfully managed by endoscopic hemostasis involving clipping and/or electrocoagulation without the necessity of any surgical interventions or blood transfusions.

PATIENT-RELATED FACTORS AND DELAYED BLEEDING

A complete comparison of patients with and without delayed bleeding is summarized in Table 2. In terms of patient-related factors, our comparison of the incidence of delayed bleeding included the following results: gender (male/female), 6.3/

Table 1. Clinicopathological characteristics of delayed bleeding cases

No.	Age	Gender	Resection method	Prophylactic clip	Interval ^a (days)	Location	Lesion size (mm)	Macroscopic type	Histopathology
1	61	F	EMR	Used	1	Transverse	25	Other	Carcinoma
2	56	M	EMR	Not	7	Ascending	25	Other	Carcinoma
3	80	M	EMR	Not	1	Rectum	20	Other	Adenoma
4	70	M	EMR	Not	10	Sigmoid	30	Other	Adenoma
5	71	M	EMR	Not	7	Sigmoid	60	Other	Carcinoma
6	79	M	EMR	Not	1	Sigmoid	20	Other	Adenoma
7	74	M	EMR	Not	1	Cecum	50	Sessile	Adenoma
8	68	M	EMR	Not	2	Cecum	40	Other	Carcinoma
9	59	M	EMR	Not	1	Transverse	25	Other	Carcinoma
10	65	M	EMR	Not	3	Transverse	30	Other	Carcinoma
11	61	M	EMR	Not	3	Ascending	35	Other	Carcinoma
12	65	M	EMR	Not	5	Rectum	25	Other	Carcinoma
13	52	F	PO	Not	1	Ascending	50	Other	Carcinoma
14	49	M	PO	Used	14	Sigmoid	28	Sessile	Carcinoma
15	64	M	EMR	Used	2	Transverse	40	Sessile	Carcinoma
16	54	M	EMR	Not	7	Descending	20	Sessile	Adenoma
17	45	M	EMR	Not	2	Rectum	20	Sessile	Carcinoma

^aBetween ER and the onset of delayed bleeding.**Table 2.** Comparison of patients with and without delayed bleeding

	Total	Delayed bleeding		P value
		Yes	No	
Number of patients	375	17	358	
Age, years (mean ± SD)	63.3 ± 12.3	63.3 ± 10.0	63.3 ± 12.4	NS
Gender (male/female)	240/135	15/2	225/133	0.04
Hypertension (+/-)	83/292	6/11	77/281	NS
Current use of anticoagulant drugs (+/-)	6/369	1/16	5/353	NS
Current use of antiplatelet drugs (+/-)	10/365	0/17	10/348	NS

NS, not significant.

1.5% ($P = 0.04$); hypertension (+/-), 7.2/3.8% ($P = 0.18$); current use of anticoagulant (+/-), 16.7/4.3% ($P = 0.24$); and current use of antiplatelet (+/-), 0/4.9% ($P = 0.53$). There was no delayed bleeding in one patient using both anticoagulant and antiplatelet drugs. There was virtually no difference between the two groups of patients with and without delayed bleeding in terms of mean age, but the delayed bleeding rate in males was significantly higher than in females.

TUMOR-RELATED FACTORS AND DELAYED BLEEDING

A complete comparison of lesions with and without delayed bleeding is summarized in Table 3. As for

tumor-related factors, our comparison of the incidence of delayed bleeding included the following results: tumor location (colon/rectum), 3.9/5.2% ($P = 0.81$); macroscopic type (sessile/other), 2.7/5.4% ($P = 0.59$); histopathological findings (adenoma/carcinoma), 3.8/4.4% ($P = 0.76$); resection method (*en bloc* resection/piece-meal resection), 3.1/5.3% ($P = 0.29$); and placement of prophylactic clips (used/not used), 1.7/6.1% ($P = 0.04$). There were no statistically significant differences between lesions with and without delayed bleeding except that the delayed bleeding rate was significantly higher in those cases without prophylactic clip placement.

Table 3. Comparison of lesions with and without delayed bleeding

	Total	Delayed bleeding		P value
		Yes	No	
Number of lesions	403	17	386	
Location (colon/rectum)	306/97	12/5	262/124	NS
Lesion size, mm (mean ± SD)	27.1 ± 9.6	31.9 ± 12.2	26.8 ± 9.5	NS
Macroscopic type (sessile/other ^a)	182/221	5/12	177/209	NS
Histopathology (adenoma/carcinoma)	132/271	5/12	127/259	NS
Resection method (<i>en bloc</i> /piecemeal)	194/209	6/11	188/198	NS
Prophylactic clip placement (used/not used)	174/229	3/14	171/215	0.04

NS, not significant.
^aFlat, depressed or recurrent.

DISCUSSION

In this study, the risk factors for delayed bleeding after ER were assessed in a group of patients specifically with large colorectal tumors which differed from previous reports. The delayed bleeding rate in male patients and those patients who did not receive prophylactic clip placement was significantly higher ($P = 0.04$).

A number of studies have attempted to identify the factors involved in the occurrence of delayed bleeding after ER, and various factors such as large size, sessile type, right-side location, hypertension and prior anticoagulation therapy have been proposed as being associated with an increased risk of delayed bleeding (15,25–31). This is the first large-scale study to assess these contributing factors in patients specifically with large colorectal tumors.

Delayed bleeding after ER is a clinically serious problem because it can lead to emergency endoscopic hemostasis, intensive patient care monitoring and/or the need for blood transfusions (12,15). Various studies have reported delayed bleeding in 0.3–6.1% of POs (12,15,28,32). In one recent investigation of 6617 POs by Watabe et al. (25), the rate of post-PO bleeding was 0.57%, but the mean size of polyps was only 5.6 mm. Our overall rate of delayed bleeding was higher undoubtedly because the mean size in this study was considerably larger at 27.1 ± 9.6 mm. The results of other studies have also indicated that polyp size was an important risk factor for bleeding both during and after a procedure (15,25–27,33,34), although there was no significant difference between cases with and without delayed bleeding for tumors ≥ 20 mm according to the results of our study.

In terms of patient-related factors, the delayed bleeding rate was significantly higher in males than females ($P = 0.04$). We could not elucidate from their medical records a possible reason why there was a gender-based difference in patients with delayed bleeding, however, because there was no available evidence regarding any lifestyle differences between male and female patients with delayed bleeding. Watabe et al.

(25) concluded that hypertension was a significant risk factor for delayed bleeding, but there was no correlation between hypertension and delayed bleeding in our study. Neither could we find a correlation between the current use of anticoagulant and/or antiplatelet drugs and delayed bleeding.

In contrast, the delayed bleeding rate was significantly lower in the group of patients with prophylactic clip placement ($P = 0.04$). Application of hemostatic clips has been proven safe and effective for managing delayed bleeding following ER (35–37). Hachisu reported on 29 patients treated with prophylactic clipping following PO and delayed bleeding was not detected in any of them (38). A recent study indicated that prophylactic clip placement for the closure of mucosal defects in cases of gastric EMR reduced delayed bleeding (39), but it is still unclear whether or not such clip placement decreases the occurrence of delayed bleeding after ER for colorectal tumors. Although the study by Shioji et al. (12) indicated that clipping did not decrease the occurrence of delayed bleeding, we believe that their study population ($n = 413$) was too small to justify such a conclusion as 76.9% of the polyps were < 10 mm (mean size, 7.8 mm). As a result, the efficacy of prophylactic clip placement for the prevention of delayed bleeding in large colorectal tumors remains uncertain and should be determined by analyzing a high-risk group.

The study by Friedland and Soetikno (40) reported that there were no bleeding episodes after resection of 41 polyps up to 10 mm in size followed immediately by prophylactic application in 21 patients receiving the long-term anticoagulation drug warfarin. Although it was a small single-center retrospective study, their findings indicated that prophylactic clip placement in a high-risk group of patients on anticoagulation medication could be effective against delayed bleeding. Our study group also involved high-risk patients because of the large mean size of the resected tumors. Hemoclips were applied to cases of immediate bleeding in our study and we were unable to separate such cases from the prophylactic clip placement cases. Although cases with

immediate bleeding would logically be expected to have a higher risk of delayed bleeding, the rate of delayed bleeding in the entire group in which clipping was performed was significantly lower. This is the first study demonstrating the efficacy of prophylactic clipping in preventing delayed bleeding for colorectal tumors ≥ 20 mm.

The fact that this also was a single-center retrospective study like the earlier Friedland and Soetikno study is the most notable limitation. A second limitation is that we cannot exclude the possibility of inter-endoscopist bias as to whether or not prophylactic clip placement was performed in individual cases.

The other significant risk factor for delayed bleeding involved male patients in our study compared with female patients. Particularly, in male patients, the delayed bleeding rate in patients without prophylactic clip placement was significantly higher (8.9%) compared with patients with prophylactic clip placement (1.8%) ($P = 0.03$). As indicated above, a recommendation from this study might be that prophylactic clipping should be performed in male patients. In contrast, however, other previously published studies have reported different risk factors for delayed bleeding including sessile type, right-side location, patient hypertension and prior or long-term anticoagulation therapy. In the future, investigation may demonstrate the effectiveness of prophylactic clip placement for patients having such risk factors. We would also have to consider the relationship if any between delayed bleeding and different clipping techniques involving complete closure or exposed vessel clipping. Consequently, the effectiveness of prophylactic clip placement after ER for large colorectal tumors needs to be confirmed in a prospective randomized multicenter trial.

In conclusion, the results of this study indicated that prophylactic clip placement may be an effective method for preventing delayed bleeding after ER for large colorectal tumors.

Authors' Contributions

S.F. and Y.S. conceived study concept and design. S.F. co-wrote the paper and analyzed the data together with T.S. and T.N. and T.M. All authors contributed to endoscopic technical support and discussed the results and commented on the manuscript.

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Conflict of interest statement

None declared.

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