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【 ORIGINAL ARTICLE 】

Perforation and Postoperative Bleeding Associated with Endoscopic Submucosal Dissection in Colorectal Tumors: An Analysis of 398 Lesions Treated in Saga, Japan

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Abstract:

Objectives The aim of this study was to clarify the safety of colorectal endoscopic submucosal dissection (ESD) during the era of health insurance coverage starting from April 2012 in Japan.

Methods Between April 2012 and May 2016, ESD was applied to 398 lesions in 373 patients. Risk factors for serious complications of colorectal ESD, perforation and post-ESD bleeding, were evaluated focusing on the resected specimen size, location, growth pattern, invasion depth, histopathology, postoperative clipping, and procedure time. In addition, the relationship between serious complications and patients' background characteristics was analyzed.

Results Among 373 patients, perforation occurred in 12 patients and post-ESD bleeding in 19 patients. A univariate analysis showed that the risk factors for perforation were the lesion size, the resected specimen size, and a long operation time. A multivariate analysis showed that a long operation time was a risk factor for perforation during colorectal ESD. A univariate analysis indicated that significant risk factors for postoperative bleeding were a long operation time, rectal lesion, and cancer. All patients with serious complications were treated by an endoscopic procedure without blood transfusion or the need to convert to open surgery.

Conclusion The present study suggests that colorectal ESD may be accepted with relative safety in Japan as a common therapeutic approach for early colorectal cancer.

Key words: serious complications, clip, colorectal cancer, multivariate analysis

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Introduction

Endoscopic mucosal resection (EMR) of colorectal lesions has become widely accepted as a standard procedure (1-7). EMR for colorectal lesions exceeding 20 mm in diameter sometimes results in piecemeal resection (8-11). Because of high recurrence rates (around 5%-20%) after piecemeal resection (12-17), en-bloc resection is required for curative treatment with an accurate histopathological evaluation (8-11). This limitation of EMR has been overcome by the development of endoscopic submucosal dissection (ESD) in the stomach and colon (18-23). However, the technical difficulty of performing ESD for colorectal lesions, given the thin intestinal wall, can induce frequent complications, particularly perforation and postoperative delayed bleeding.

Since June 2009, colorectal ESD has been performed in Japan in accordance with the advanced medical treatment system approved by the Japanese Ministry of Health, Labour and Welfare. Colorectal ESD was distinguished from gastric and esophageal ESD because of the associated high complication rates. In April 2012, however, colorectal ESD was in-

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cluded in health insurance coverage in Japan because of the accumulation of experience with a relatively low complication rate under advanced medical treatment systems (19, 24). Since colorectal ESD was approved for health insurance coverage in April 2012, ESD for colorectal lesions has been applied more often in Japan.

The assessment and prediction of risks of complications after health insurance coverage in Japan may provide important, useful information for colorectal ESD. Several studies have assessed the risk factors for perforation during colorectal ESD and postoperative bleeding (25-32), but few have assessed the risk factors for complications after health insurance coverage started in Japan (24). The aim of the present study was to clarify the safety of colorectal ESD in Japan after April 2012.

Patients and Methods

Patients

Between April 2012 and May 2016, colorectal ESD was performed for 398 lesions in 381 patients in Saga Medical School and Saga-ken Medical Centre Koseikan: 250 lesions in Saga Medical School and 148 lesions in Saga-Ken Medical Centre Koseikan. All lesions were treated under the Japanese national health insurance system. The indications for ESD for colorectal lesions were identical to those established in previous reports from other institutions (1, 33, 34) with Japanese health insurance. The pre-operation indications for ESD were the presence of colorectal neoplasms with a tumor size of 2-5 cm. Indications were determined with magnifying endoscopy and included the following characteristics:

·Large (>20 mm in diameter) lesions (possibly indicated for endoscopic treatment but difficult to treat with en-bloc resection using the snare device), including lesions suspected of having submucosal invasion and/or exhibiting the Vi pit pattern with magnifying endoscopy

·Mucosal lesions with fibrosis

·Local residual early cancer after endoscopic resection

·Sporadic localized tumor with chronic inflammation, such as ulcerative colitis

ESD procedures

ESD was performed using the following procedures, as previously described (19, 21): Hypertonic sodium epinephrine and/or sodium hyaluronate were injected into the submucosal layer around the lesion to raise the mucosal layer. An incision into the mucosa was performed outside the target lesion. The subsequent submucosal dissection of the lesion was performed with a Dual Knife (Olympus Medical Systems Co., Ltd., Tokyo, Japan) and/or a Flush Knife-BT (ball tip; Fujifilm Co., Ltd., Tokyo, Japan). Regarding anticoagulants and/or antiplatelet drugs, their continued use or cancellation was decided according to the Japan Gastroenterological Endoscopy Society (JGES) guidelines (35, 36).

Perforation during ESD and postoperative bleeding

Perforation was diagnosed endoscopically and/or by the presence of free air on plain radiography and/or computed tomography (CT) just after ESD. Perforations detected during the ESD procedure were immediately closed with a metal clip (37), and the patient was given antibiotics. Postoperative bleeding was defined as clinical evidence of bleeding after ESD requiring special measures for hemostasis and/or decreases in the hemoglobin level by ≥2.0 g/dl in comparison with the last preoperative level (38). Bleeding during the ESD procedure was not considered postoperative bleeding.

Data analyses

The clinical record, endoscopic images, endoscopic report, and histopathological report were reviewed for all patients. Patients with perforation or postoperative bleeding were retrospectively evaluated regarding the following factors: i) patient-related factors, including sex, age and daily usage of anticoagulants and/or antiplatelet drugs; ii) tumor- and treatment-related factors, including the location of the tumor, the size of the resected specimens, and the operation time; iii) co-morbidities, including cerebrovascular disease, ischemic heart disease, chronic liver damage, chronic renal failure, hyperuricemia, hypertension, and diabetes mellitus.

Data were analyzed using the χ^2 test followed by a multivariate logistic regression analysis to evaluate the effects of independent variables with adjustments for the effects of each of the other factors with the IBM SPSS Statistic software program (International Business Machines Corporation, Armonk, NY, USA). Differences of $p<0.05$ were considered significant.

Results

The characteristics of all patients who underwent ESD for colorectal lesions under the Japan national health insurance system during 2012-2016 were as follows (Table 1): mean age 68.7±9.9 years (range 25-90 years); resected specimen size 35.0±13.6 mm (range 23-65 mm); and operation time 74.0±56.2 minutes (range 20- 427 minutes). Perforation during ESD occurred in 12 of the 398 patients (3.0%). All patients with perforation were treated by endoscopic clipping without the need for laparotomy. The perforation rate was not affected by age, sex, or the use of anticoagulants and/or antiplatelet drugs.

Tumor and treatment-related factors of perforation during ESD are shown in Table 2. A univariate analysis indicated that both the lesion size (28.3 vs 38.4 mm, $p<0.05$) and the resected specimen size (34.8 vs 44.5 mm, $p<0.05$) were significantly larger in patients with perforation. The operation time for ESD was significantly longer in patients with perforation (71.4 vs 159.2 minutes, $p<0.05$). The operation time included the time for intraoperative hemostasis and the time for clipping to close intraoperative perforation. The tumor

Table 1. Results of a univariate analysis of patient-related factors for perforation during colorectal endoscopic submucosal dissection.

Characteristics	Total	Perforation (+)	Perforation (-)	p
Number of patients	398	12 (3%)	386 (97%)	
Age (years; mean±SD)	68.7±9.9	70.8±8.1	68.6±10	N.S.
Sex				
Male	249	5 (2.0%)	244 (98.0%)	N.S.
Female	149	7 (4.7%)	142 (95.3%)	
Anticoagulants and/or antiplatelet drugs				
(+)	50	3 (6%)	47 (94%)	N.S.
(-)	348	9 (2.6%)	339 (97.4%)	

SD: standard deviation, N.S.: not significant

Table 2. Results of a Univariate Analysis of Tumor- and Treatment-related Factors for Perforation during Colorectal Endoscopic Submucosal Dissection.

Factors	Total	Perforation (+)	Perforation (-)	p
Number of patients	398	12	387	
Tumor location				
Colon	290	10 (3.4%)	280 (96.6%)	N.S.
Rectum	108	2 (1.9%)	106 (98.1%)	
Lesion size (mm)	28.6±14.2	38.4±13.8	28.3±14.1	<0.05
Resected size (mm)	35.0±13.6	44.5±15.2	34.8±13.5	<0.05
Operation time (min)	74.0±56.2	159.2±119.8	71.4±51.2	<0.05
Invasion morphology				
Superficial	328	8 (2.4%)	320 (97.6%)	N.S.
Protruded	69	4 (5.8%)	65 (94.2%)	
Histological type				
Adenoma	208	3 (1.4%)	205 (98.6%)	N.S.
Cancer	189	9 (4.8%)	180 (95.2%)	
Closure with hemoclips				
Yes	129	6 (4.7%)	123 (95.3%)	N.S.
No	269	6 (2.2%)	263 (97.8%)	

N.S.: not significant

location, invasion depth, histological type, and closure with a hemoclip were not risk factors for perforation during ESD. Table 3 indicates whether or not perforation during ESD was exacerbated by co-morbidities, including cerebral vessel disease, ischemic heart disease, chronic liver damage, chronic renal dysfunction, hyperuricemia, hypertension, and diabetes mellitus. These co-morbidities were not risk factors for perforation during ESD. A multivariate logistic regression analysis in Table 4 revealed that a long operation time was an independent risk factor for perforation ($p<0.001$).

Post-ESD operative bleeding occurred in 19 of the 398 patients (4.8%). All cases of postoperative bleeding were successfully treated by an endoscopic procedure that entailed metal clipping and/or electrocoagulation. As indicated in Table 5, sex, age, and the use of anticoagulants and/or antiplatelet drugs were not risk factors for post-ESD bleeding.

Table 6 shows the tumor- and treatment-related factors of postoperative bleeding associated with ESD. A univariate analysis indicated that the tumor location (colon 3.1% vs. rectum 9.3%, $p<0.05$), histological type (adenoma 1.9% vs. adenocarcinoma 7.9%, $p<0.05$), and closure with a hemoclip ("yes" 0.8% vs. "no" 6.7%, $p<0.05$) were significantly associated with post-ESD bleeding. A large lesion size (28.2 vs. 35.6 mm, $p<0.05$) and the long ESD operation time (71.6 vs. 123.0 minutes, $p<0.05$) were risk factors for post-ESD bleeding. Postoperative bleeding associated with ESD was influenced by neither the invasion depth nor the resected size. As indicated in Table 7, post-ESD bleeding was not affected by co-morbidities, including cerebral vessel diseases, ischemic heart disease, chronic liver damage, chronic renal dysfunction, hyperuricemia, hypertension, or diabetes mellitus, indicating that these co-morbidities were not risk factors for postoperative bleeding. As shown in Table 8, a multivariate logistic regression analysis revealed that a long ESD operation time, a rectal lesion, and histological malignancy were independent risk factors for post-ESD bleeding ($p<0.05$ for each).

The complication rate of the trainees, who had experi-

Table 3. Results of a Univariate Analysis of Co-morbidities in Patients with Perforation during Colorectal Endoscopic Submucosal Dissection.

Factors	Total	Perforation (+)	Perforation (-)	p
Number of patients	398	12	387	
Cerebral vessel diseases				
(+)	30	0	30 (100%)	N.S.
(-)	368	12 (3.3%)	356 (96.7%)	
Ischemic heart disease				
(+)	46	3 (6.5%)	43 (93.5%)	N.S.
(-)	352	9 (2.6%)	343 (97.4%)	
Chronic liver damage				
(+)	23	2 (8.7%)	21 (91.3%)	N.S.
(-)	375	10 (2.7%)	365 (97.3%)	
Chronic renal dysfunction				
(+)	14	2 (14.3%)	12 (85.7%)	N.S.
(-)	384	10 (2.6%)	374 (97.4%)	
Hyperuricemia				
(+)	31	2 (6.5%)	29 (93.5%)	N.S.
(-)	367	10 (2.7%)	357 (97.3%)	
Hypertension				
(+)	171	5 (2.9%)	166 (97.1%)	N.S.
(-)	227	7 (3.1%)	220 (96.9%)	
Diabetes mellitus				
(+)	51	2 (3.9%)	49 (96.1%)	N.S.
(-)	347	10 (2.9%)	337 (97.1%)	

N.S.: not significant

Table 4. Results of a Multivariable Logistic Regression Analysis of Factors Associated with Perforation during Colorectal Endoscopic Submucosal Dissection.

Variable	Odds ratio	95% CI	p
Lesion size	-		N.S.
Operation time	-		<0.001
Closure with hemoclip	3.49	0.96- 12.71	0.058

CI: confidence interval, N.S.: not significant

enced less than 50 ESD cases, was 10.7% (perforation 2.4%, 2/84 cases; postoperative bleeding 8.3%, 7/84 cases), which was not significantly higher than that of the experienced endoscopists. The mean operation time of the trainees was 87.5 minutes, which was relatively long, but not significantly longer than that of the experienced surgeons.

Discussion

This study evaluated the rates of serious complications (perforation 3.0%, 12/398 cases; postoperative bleeding 4.8%, 19/398 cases) following colorectal ESD in Saga, Japan. The rate of perforation during colorectal ESD was reported to be 1.4%-10.4% (26-33, 39-44). The complication rate was high during the early period when ESD was performed in a clinical study in 2007 (10.4%) (43). When colorectal ESD was performed in accordance with the advanced medical treatment system (No. 78) approved by the Japanese Ministry of Health, Labour and Welfare in June 2009, however, the rate of perforation was lower, as the procedure was performed cautiously and only by experienced endoscopists. Most studies that reported perforation associated with ESD in Japan included subjects who received the procedure under the advanced medical treatment system (2009-2012), and the number of such subjects under health insurance coverage since 2012 was limited. In this study, the perforation rate was almost equivalent to that in other reports (26-34, 39-47). All cases with perforation in this study were treated conservatively with endoscopy, as previously reported in other institutes (26-32, 36-49).

The rate of postoperative bleeding in colorectal ESD was reported to be 0%-12.0% (15, 16, 31, 32, 39-45). The report with the highest complication rate (12.0%) included subjects with mild bleeding that did not require endoscopic hemostasis (44). The rate of postoperative bleeding in other studies ranged from 0% to 12.0% (15, 16, 31, 32, 39-45), which was slightly higher than in the present study. The present study included patients who required endoscopic hemostasis. The reason for the relatively low rate of postoperative bleeding was unclear, as prophylactic endoscopic therapy for bleeding was not applied routinely in the present study. All patients with bleeding in the present study were treated by the endoscopic procedure (1, 50) without blood transfusion or a need to convert to a surgical operation.

The serious complication rates, including perforation and

Table 5. Results of a Univariate Analysis of Patient-related Factors in Postoperative Bleeding after Colorectal Endoscopic Submucosal Dissection

Factors	Total	Present	Absent	p
Number of patients	398	19	379	
Age (years), mean±SD	68.7±9.9	69.1±7.2	68.7±10.1	N.S.
Sex				
Male	249	11 (4.4%)	238 (95.6%)	N.S.
Female	149	8 (5.4%)	141 (94.6%)	N.S.
Anticoagulants and/or antiplatelet drugs				
Yes	50	2 (4%)	48 (96%)	N.S.
No	348	17 (4.9%)	331 (95.1%)	N.S.

SD: standard deviation, N.S.: not significant

Table 6. Results of a Univariate Analysis of Tumor- and Treatment-related Factors and Postoperative Bleeding after Colorectal Endoscopic Submucosal Dissection.

Factors	Total	Present	Absent	p
Number of patients	398	19	379	
Tumor location				
Colon	290	9 (3.1%)	281 (96.9%)	<0.05
Rectum	108	10 (9.3%)	98 (90.7%)	
Lesion size (mm)		35.6±20.2	28.2±13.7	<0.05
Resected size (mm)		40.7±19.8	34.8±13.2	N.S.
Operation time (min)		123.0±108.5	71.6±51.4	<0.05
Invasion morphology				
Superficial	328	13 (4.0%)	315 (96%)	*N.S.*
Protruded	69	6 (8.7%)	63 (91.3%)	
Histological type				
Adenoma	209	4 (1.9%)	205 (98.1%)	<0.05
Carcinoma	189	15 (7.9%)	174 (92.1%)	
Closure with hemoclips				
Yes	129	1 (0.8%)	128 (99.2%)	<0.05
No	269	18 (6.7%)	251 (93.3%)	

N.S.: not significant

bleeding, in colorectal ESD performed by trainees described in several reports in Japan have been controversial (46, 51-53); however, the operation time of the trainees was relatively long during the ESD procedure in all of these papers. The serious complication rates of the trainees in the present study were not different in 84 out of the 381 colorectal ESD patients, in whom ESD was performed under the coaching of experienced endoscopists. As a result, the rates of serious complications among the trainees in the present study did not differ substantially from those observed for experienced endoscopists.

The present study indicated that the serious complications of perforation and postoperative bleeding occurred in about 5% of patients associated with the colorectal ESD. All patients with serious complications were treated by endoscopic procedures, which indicated that colorectal ESD under health insurance coverage was a relatively safe procedure. The risk factor for perforation was a prolonged procedure time, and the risk factors for postoperative bleeding were a prolonged procedure time, tumor location in the rectum, and definitive colon cancer with a pathological diagnosis. Previous studies indicated several risk factors for serious complications with the colorectal ESD including the tumor location, fibrosis of the lesion, difficult endoscopic operability, and rich vascularity (27, 40, 47, 51, 54-62) The present retrospective study did not indicate these factors to be risk factors for serious complications, so further studies may be required to assess the reasons for the discrepancies in these findings. A prolonged procedure time being recognized as a risk factor in the present study was probably due to the difficulties associated with ESD, including those based on the tumor location, fibrosis, and difficult endoscopic operability, as previously reported.

In conclusion, most of the previous studies in Japan included patients who underwent colorectal ESD under special conditions in particular hospitals. The present study suggested that colorectal ESD may be relatively safely applied to treat early colorectal cancer as a common therapeutic ap-

Table 7. Results of a Univariate Analysis of Co-morbidities in Patients with Postoperative Bleeding after Colorectal Endoscopic Submucosal Dissection.

Co-morbidity	Total	Present	Absent	p
Number of patients	398	19	379	
Cerebral vessel diseases				
(+)	30	2 (6.7%)	28 (93.3%)	N.S.
(-)	368	17 (4.6%)	351 (95.4%)	
Ischemic heart disease				
(+)	46	2 (4.3%)	44 (95.7%)	N.S.
(-)	352	17 (4.8%)	335 (95.2%)	
Chronic liver damage				
(+)	23	3 (13%)	20 (87%)	N.S.
(-)	375	16 (4.3%)	359 (95.7%)	
Chronic renal dysfunction				
(+)	14	2 (14.3%)	12 (85.7%)	N.S.
(-)	384	17 (4.4%)	367 (95.6%)	
Hyperuricemia				
(+)	31	2 (6.5%)	29 (93.5%)	N.S.
(-)	367	17 (4.6%)	350 (95.4%)	
Hypertension				
(+)	171	8 (4.7%)	163 (95.3%)	N.S.
(-)	227	11 (4.8%)	216 (95.2%)	
Diabetes mellitus				
(+)	51	3 (5.9%)	48 (94.1%)	N.S.
(-)	347	16 (4.6%)	331 (95.4%)	

N.S.: not significant

Table 8. Results of a Multivariable Logistic Regression Analysis of Factors Associated Postoperative Bleeding after Colorectal Endoscopic Submucosal Dissection.

Variable	Odds ratio	95% CI	p
Operation time	-		0.006
Location (rectum)	2.69	1.02-7.06	0.045
Histological type (carcinoma)	3.4	1.08-10.71	0.037

CI: confidence interval

proach.

The authors state that they have no Conflict of Interest (COI).

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