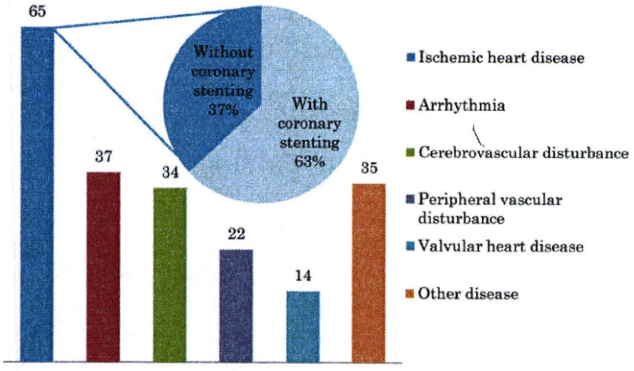

Fig. 1. Comorbidities of 208 patients taking anticoagulants or antiplatelet agents. Among 65 patients with ischemic heart disease, 41 patients (63%) had a mechanical stent in the coronary artery.

Cessation period

Histograms of cessation periods before and after endoscopy are shown in Figures 2 and 3, respectively. Most patients underwent endoscopy without cessation or after a cessation period of 6–7 days. For details, patients receiving single antithrombotic therapy tended to undergo endoscopy after a cessation period of 6–7 days principally, and patients receiving combined antithrombotic therapy tended to undergo endoscopy without cessation. However, patients who underwent endoscopy with invasive procedures after the cessation period tended to restart antithrombotic therapy the next day after endoscopy.

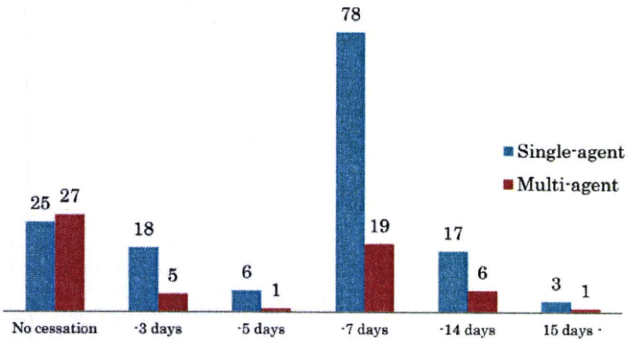

Fig. 2. Preoperative cessation period of patients receiving single-agent or multi-agent antithrombotic therapy. Among 208 patients, 206 patients sent back valid responses to our questionnaire on preoperative cessation periods.

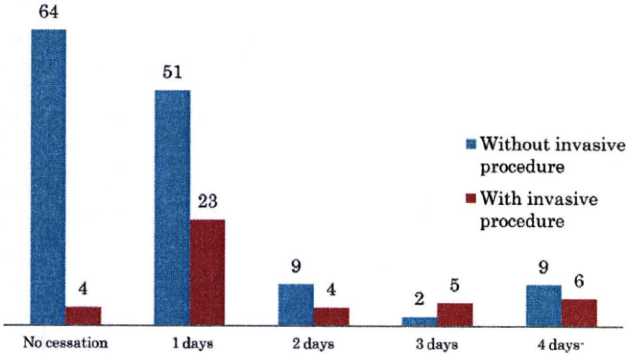

Fig. 3. Postoperative cessation period of patients who underwent invasive or non-invasive procedures. Among 208 patients, 177 patients sent back valid responses to our questionnaire on postoperative cessation periods.

Specialty of doctors who determined cessation periods

Cessation periods before endoscopy were determined by cardiology specialists for 57.7% of the patients. For only 4.8% of the patients, cessation periods before endoscopy were determined by gastroenterological specialists (Fig. 4). By contrast, for 36.5% of the patients, cessation periods after endoscopy were determined by gastroenterological specialists, including operators of endoscopes.

Complications

In this study, no symptom related to thromboembolic events and gastrointestinal bleeding was observed. No patients underwent invasive procedures without cessation.

DISCUSSION

In our previous study, we revealed the low permeation of the JGES guidelines in the cessation period of aspirin alone, ticlopidine alone and the combination of both. Most patients receiving aspirin alone or ticlopidine alone underwent endoscopy after a cessation period of 6–7 days. Among patients receiving the combination of aspirin and ticlopidine, most patients underwent endoscopy without cessation. These results indicated a large discrepancy between the clinical daily practice and the recommendations of the JGES guidelines. The present study also revealed this discrepancy.

Considering the results of the present study, the low permeation of the guidelines is caused by the daily clinical practice that cessation periods are mainly determined by prescribing doctors with non-gastroenterological specialties. Furthermore, this means that risk estimation of comorbidities for cessation is principally left to prescribing doctors. The present study revealed the limitations of the guidelines for gastroenterology specialists themselves to decide cessation periods considering comorbidities. We propose that enhancement of coordination between various specialists is mandatory to manage anticoagulants and antiplatelet agents appropriately.

The present study also revealed the current daily practice of the cessation period after endoscopy. In the JGES guidelines, restarting antithrombotic therapy is recommended shortly after endoscopy as far as low risks of bleeding are confirmed after endoscopy. However, there are no solid criteria to judge whether or not risks of bleeding are low. In the present study, 74 patients, including 23 patients who underwent invasive procedures, restarted antithrombotic therapy the next day after endoscopy. Considering that they all did not experience gastrointestinal bleeding after endoscopy, restarting the next day after endoscopy may be reasonable.

Still, we have another problem, which is the necessity for cessation before minimally invasive biopsy. Although

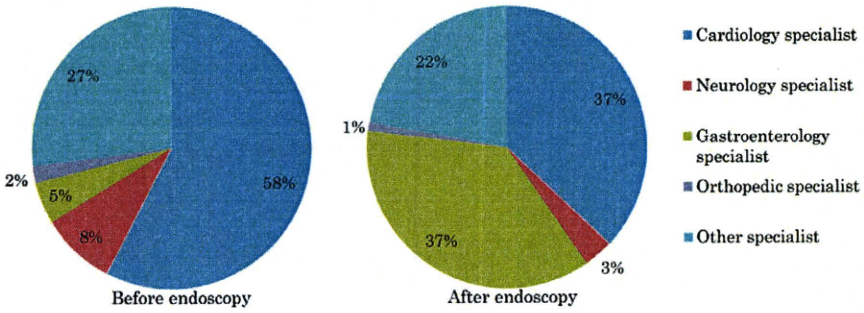

Fig. 4. Specialties of doctors who determined cessation periods before and after endoscopy.

Western guidelines recommend biopsy without cessation, Japanese physicians principally secure cessation before biopsy and the JGES guidelines also recommend this. We speculate that the most important reason is racial differences, as mentioned in the JGES guidelines.[11] However, after invasive procedures, thromboembolic events during cessation are reported to result in lethal outcomes rather than bleeding events.[15] Additionally, there are not enough data on racial differences to conclude that bleeding events are more life-threatening than thromboembolic events for Japanese compared to Western people. Although we need further accumulation of data concerning this problem, minimally invasive biopsy without cessation might be acceptable for Japanese.

Taken as a whole, the present study revealed further details of clinical daily practice concerning the management of anticoagulants and antiplatelet agents for scheduled endoscopy. However, it has some limitations. To exclude selection bias in a single-center design and insufficient number of patients, we need further investigation in a multi-center design. We do believe that in a few years it will be possible to correct the current gap between endoscopists and non-gastroenterological specialists in the management of anticoagulants and antiplatelet agents for scheduled endoscopy.

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A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding

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Background: Endoscopic submucosal dissection (ESD) is one of the curative endoluminal surgical procedures for gastric epithelial neoplasms. There has been little research on bleeding after gastric ESD.

Objective: To investigate cases of post-ESD bleeding and to verify whether a second-look endoscopy after ESD is effective in the prevention of delayed bleeding.

Design: A retrospective study with consecutive data.

Setting: A single tertiary referral center.

Subjects: A total of 454 gastric epithelial neoplasms (386 early gastric cancers and 68 gastric adenomas).

Interventions: ESD and second-look endoscopy.

Main Outcome Measurements: Predictors on post-ESD bleeding by univariate analysis, incidence of post–ESD bleedings, and the timing of those before and after second-look endoscopy.

Results: Post–ESD bleeding occurred in 26 (5.7%) lesions. Gross type (flat or depressed type) was the only factor influencing post-ESD bleeding. All cases of post-ESD bleeding occurred within 14 days after ESD (median 2; range 0-14), and bleeding tended to occur from the lower and upper stomach earlier and later, respectively. In 19 lesions with delayed bleeding more than 24 hours after ESD, the maximum delayed bleeding rates before and after the second-look endoscopy were 2.8% and 2.5%, respectively.

Limitations: A retrospective, single-center analysis.

Conclusions: A second-look endoscopy after gastric ESD may contribute little to the prevention of delayed bleeding. (Gastrointest Endosc 2010;71:241-8.)

Endoscopic submucosal dissection (ESD) has been increasingly established as a promising endoluminal technique for GI epithelial neoplasms. Unlike conventional techniques such as EMR, ESD consists of circumferential mucosal incision and submucosal dissection, which have made it possible, even in a large tumors or tumors with ulcerative findings, to resect in en bloc fashion with tumor-free margins.[1-5] By using ESD, we have performed curative resection for node-negative early gastric cancer (EGC)[6] instead of open surgery.

One of the major concerns about gastric ESD is postoperative bleeding. It occurs in approximately 5% of the patients who undergo gastric ESD.[7-10] In almost all cases, endoscopic hemostasis is effective in stopping bleeding if an emergency endoscopy is properly performed. Therefore, it is necessary to determine the nature of the post-ESD bleeding and the appropriate management. In practice, a second-look endoscopy is routinely performed the next day or later after ESD in most hospitals in Japan to check for the possibility of postoperative bleeding. However, performing a second-look endoscopy without any signs of bleeding has not yet been validated, and, to the contrary, bleeding even after the confirmation of hemostasis sometimes occurs. Because there have been few reports concerning post-ESD bleeding or its

Abbreviations: EGC, early gastric cancer; ESD, endoscopic submucosal dissection; GA, gastric adenoma; PPI, proton pump inhibitor.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2009.08.030

prevention,[10] we retrospectively reviewed our gastric ESD cases to verify the clinicopathological features of post-ESD bleeding and to confirm whether a second-look endoscopy was necessary for preventing delayed bleeding.

PATIENTS AND METHODS

A total of 476 lesions with a histologic diagnosis of gastric epithelial neoplasms (406 EGCs and 70 gastric adenomas [GAs]) were consecutively treated with ESD in our hospital from December 2003 to November 2008. Among them, 454 lesions (386 EGCs and 68 GAs) were included after exclusion of 14 lesions in a remnant stomach after gastrectomy or in a gastric tube after esophagectomy and 8 lesions in which perforation occurred during ESD caused by their specific physiological conditions.

ESD was principally indicated for possible node-negative EGCs according to the criteria of Gotoda et al[6] based on endoscopic findings including chromoendoscopy with biopsy. In cases of possible node-positive EGCs, ESD was only indicated when the lesions were considered to be technically removable from the gastric wall and patients desired to undergo ESD after sufficient information was provided by both endoscopists and surgeons. In cases of GAs, ESD was only indicated when it was possible that the lesion contained foci of cancer or the patients strongly desired the lesion to be resected. All patients provided written informed consent before undergoing treatment.

ESD procedures

The ESD technique was described elsewhere.[1-5] In brief, after circumferential marking, submucosal injection was performed below the tumor to create a submucosal fluid cushion. Next, circumferential cutting of the mucosal layer with muscularis mucosa approximately 5 mm outside the marking was performed. Subsequently, the submucosal layer beneath the tumor was dissected to detach it from the gastric wall. A mixture of 10% glycerin, 5% fructose, and 0.9% saline solution (Glyceol; Chugai Pharmaceutical Co, Tokyo, Japan) containing 0.005% indigo carmine and 0.0005% epinephrine was used as submucosal fluid.[11] Hyaluronic acid was additionally used when the lesion could not rise enough by using Glyceol alone.[12,13] The Flexknife (KD-630L; Olympus, Tokyo, Japan) was selected as the main electrosurgical knife.[3,14] Other knives, such as the IT knife (KD-610L; Olympus),[1,2] Hookknife (KD-620LR; Olympus),[4] Splash-needle (DN-2618A; Pentax, Tokyo, Japan),[5] and a needle-knife, were used in some cases instead of the Flexknife, according to the tumor characteristics and/or operator preference. Hemostatic forceps (HDB2422 W; Pentax) were used for bleeding during ESD or for visible vessels on the mucosal defect after removal.[15]

Capsule Summary

What is already known on this topic

- Endoscopic submucosal dissection (ESD) facilitates en bloc resection with tumor-free margins in gastric cancers but is associated with a postoperative bleeding rate of 5%.

What this study adds to our knowledge

- In a retrospective study of 454 cases of gastric ESD, postoperative bleeding occurred in 26, all within 14 days.
- Delayed bleeding rates before and after the second-look endoscopy were 2.8% and 2.5%, respectively.

The patient was usually allowed to eat a light meal the day after ESD. In principle, a second-look endoscopy was performed once within 1 week to check whether there was a recent hemorrhage or a possible bleeding spot (a nonbleeding visible vessel) that should be treated on the mucosal defect. The day of the second-look endoscopy was decided by the operator according to the patient's condition or the operation day once during the hospitalization. If the hospitalization was uneventful, patients were discharged within 1 week after ESD. Principally, the patients receiving anticoagulants and/or antiplatelet drugs were instructed to stop taking them for 1 week before and 1 week after ESD. When bleeding or nonbleeding visible vessels were seen (sometimes in removing adherent clots by forceps or water jet) on the second-look endoscopy, prophylactic hemostasis was performed. Clipping with hemostatic clips (HX-610-135 or HX-610-090L; Olympus) was performed for large nonbleeding vessels, and thermocoagulation with hemostatic forceps was performed for bleeding vessels or small nonbleeding vessels or in locations where it was difficult to place a clip because of consolidation of the ulcer bed. Between the day of ESD and the first day of feeding (2 days in most cases), 20 mg omeprazole twice daily was administered intravenously. Thereafter, from the day of feeding to at least 2 weeks after ESD, according to the decision of physicians in charge, one of the following proton pump inhibitors (PPIs) was administered orally: 10 mg rabeprazole, 20 mg omeprazole, or 30 mg lansoprazole once daily (these were thought to be equally effective for acid suppression).[16] A follow-up endoscopy was performed 2 months after ESD. Patients were also asked to contact the physicians in case of hematemesis or melena, even after discharge. When perforation or post-ESD bleeding occurred, the schedules for discharge including food intake were changed according to the patient's condition. In cases of possible post-ESD bleeding, the patient underwent an emergency endoscopy, and endoscopic hemostasis was performed on bleeding spots or nonbleeding visible vessels, mainly by clipping or thermocoagulation.

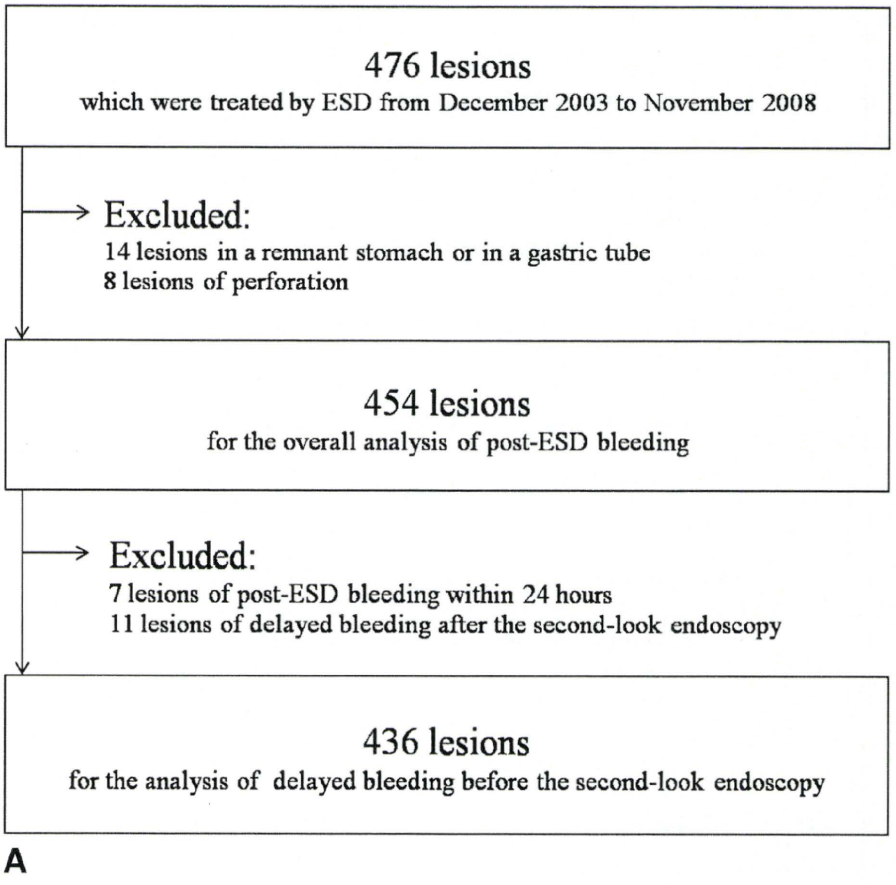

Figure 1. A, Flowchart showing the inclusion in the analysis of delayed bleeding before the second-look endoscopy. **B,** Flowchart showing the inclusion in the analysis of delayed bleeding after the second-look endoscopy. (Continued on next page)

Data analysis

Post-ESD bleeding was defined as massive bleeding from the mucosal defect after ESD, as diagnosed by the emergency endoscopy, which was performed because of hematemesis or melena. To investigate factors influencing post-ESD bleeding, the following variables were analyzed: age, sex, comorbidities (hypertension, diabetes mellitus, heart disease, chronic renal failure, and liver cirrhosis), and the use of anticoagulants and/or antiplatelet drugs (patient-related factors); the location (upper third, middle third, or lower third), circumference (anterior wall, posterior wall, lesser curve, or greater curve), gross type (0-I/IIa, 0-IIb/IIc, or combined type), ulcerative findings in the submucosal layer (endoscopically present or absent), the resection style (en bloc or piecemeal), tumor size (maximum diameter of the resected tumor actually measured), tumor depth (mucosal tumor or submucosal invasive tumor), and histologic type (intestinal type, diffuse type, or adenoma) (lesion-related factors); the period of ESD (early [2003-2005] and late [2006-2008]); and the operator's experience with gastric ESD ($\leq$30 cases, 31-100 cases, and $>$100 cases) (operator-related factors).

Delayed bleeding was defined as post-ESD bleeding diagnosed more than 24 hours after ESD. From the consecutive cases, rates of overall post-ESD bleeding and delayed bleeding before and after the second-look endoscopy were investigated to determine the usefulness of the second-look endoscopy. The maximum follow-up duration was 56 days when almost all the artificial ulcers were considered to be cured.[17] Flow charts for inclusion in each analysis are shown in Figure 1.

Statistical analysis

Univariate analysis was performed by using the Student *t* test for age and tumor size; the Fisher exact test for probability for sex, comorbidities, the use of anticoagulants and/or antiplatelet drugs, ulcerative findings, resection style, tumor depth, and the period of ESD; and the χ^2 test for location, circumference, gross type, histologic type, and the operator's experience. Statistical significance was set at a P value of $<.05$, and if there were more than 1 predictor with a significant difference by univariate analysis, multivariate analysis by using a logistic regression

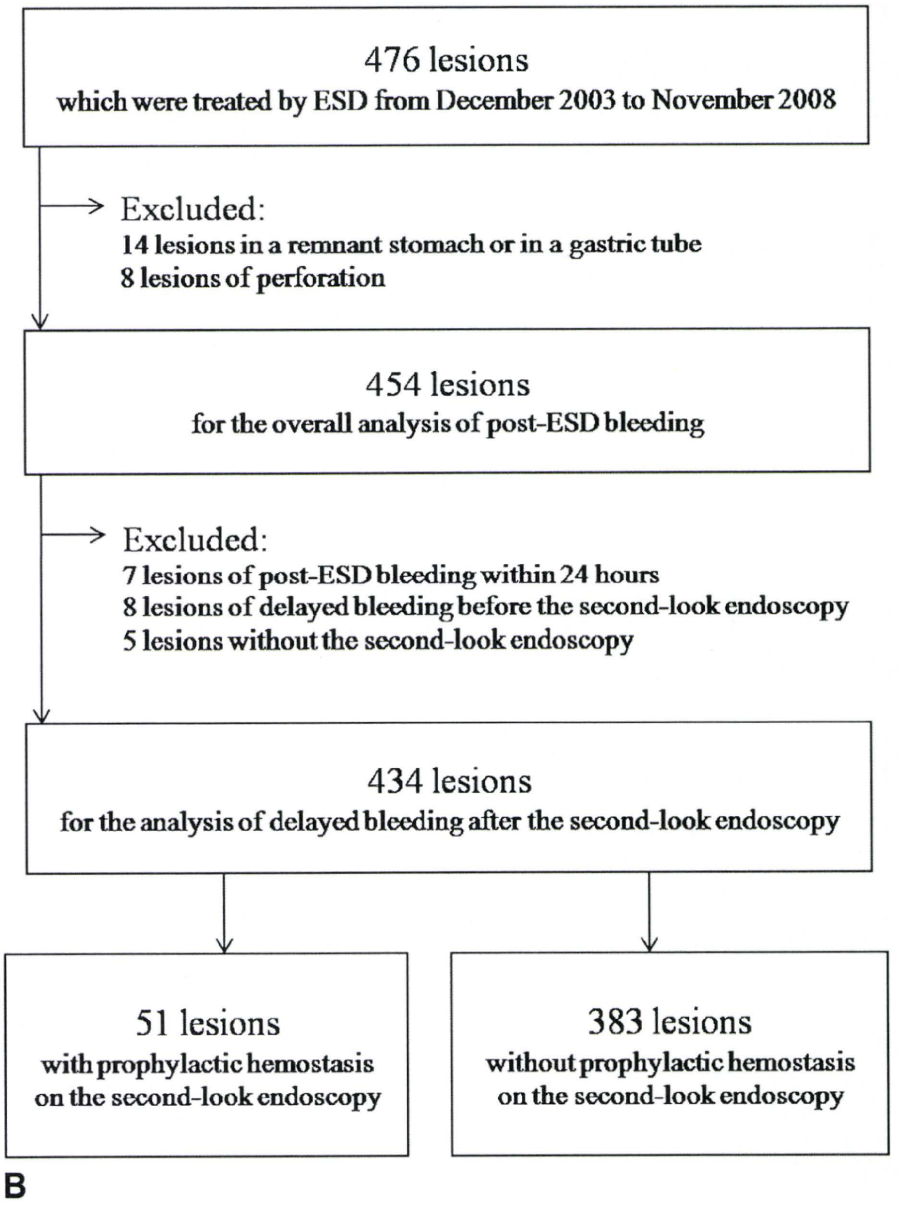

Figure 1 *(Continued)*

model was planned. The analyses of post-ESD bleeding were performed by using the Kaplan-Meier method.

RESULTS

Post-ESD bleeding occurred in 26 (5.7%) of 454 lesions. All the occurrences of bleeding were successfully managed with only endoscopic treatment, and no surgical intervention was required. No post-ESD bleeding was followed by rebleeding. In 8 (1.8%) lesions, a blood transfusion was performed.

The univariate analysis of variables for post-ESD bleeding is shown in Table 1. Only gross type (0-IIb/IIc) was considered the predictor for post-ESD bleeding with a significant difference ($P = .0376$). Multivariate analysis was not performed because there was only 1 predictor demonstrated by the univariate analysis.

All of the post-ESD bleedings occurred within 14 days after ESD (median 2; range 0-14), as shown in Figure 2. All cases of bleeding could be classified into 2 groups: the early bleeding group (16 cases) and the late bleeding group (10 cases), as shown in Figure 3. The early bleeding group had more occurrences of bleeding in the lower

TABLE 1. Univariate analysis of predictors on post–endoscopic submucosal dissection bleeding

Factors	Post-ESD bleeding		*P* value
	Occurred (26 cases)	Did not occur (428 cases)	
Patient-related			
Age (y), mean ± SD	70.6 ± 9.1	68.2 ± 9.2	.1945
Sex (male/female)	19/7	328/100	.6398
Comorbidities			
Hypertension (present/absent)	8/18	97/331	.3423
Diabetes mellitus (present/absent)	2/24	37/391	>.9999
Heart disease (present/absent)	4/22	35/393	.2651
Chronic renal failure (present/absent)	1/25	5/423	.2994
Liver cirrhosis (present/absent)	3/23	15/413	.0766
Anticoagulants/platelets (used/not used)	5/21	52/376	.3533
Lesion-related			
Location (U/M/L)	6/8/12	88/147/193	.9172
Circumference (AW/GC/LC/PW)	5/3/11/7	77/72/168/111	.9184
Gross type (I-IIa/ IIb-IIc/combined)	4/21/1	157/236/35	.0376*
Ulcerative findings (present/absent)	5/21	47/381	.2028
Resection style (en bloc/piecemeal)	24/2	419/9	.1262
Tumor size, mm (mean ± SD)	22.7 ± 17.2	18.7 ± 13.1	.1402
Tumor depth (mucosa/submucosa)	21/5	353/75	.7925
Histologic type (intestinal/diffuse/adenoma)	25/0/1	348/13/67	.1550
Operator-related			
Period of ESD (early/late)†	12/14	212/216	.8408
Operator experience (<30/31-100/>100)	8/6/12	144/84/200	.9005

ESD, Endoscopic submucosal dissection; *SD*, standard deviation; *U*, upper third; *M*, middle third; *L*, lower third; *AW*, anterior wall; *GC*, greater curve; *LC*, lesser curve; *PW*, posterior wall.
*Significantly different (IIb/IIc vs I/IIa).
†Early, 2003-2005; late, 2006-2008.

third of the stomach, and the late bleeding group had more occurrences of bleeding in the upper third (Table 2).

The median duration between ESD and the second-look endoscopy was 4 days (range 1-8), and it was performed most frequently the day after ESD. Among 19 cases of delayed bleeding, 8 and 11 occurred before and after the second-look endoscopy, respectively. No bleeding was found only on the second-look endoscopy. In 11 cases of delayed bleeding after the second-look endoscopy, red dots were seen in 5, black dots in 3, and clean ulcers without clots in 3 on the second-look endoscopy. Bleeding spots could be retrospectively matched to the dots on the ulcer on the second-look endoscopy in 7 cases, but there were no signs identified before bleeding in 4 cases.

Of 51 and 383 cases with and without prophylactic hemostasis, respectively, delayed bleeding after the second-look endoscopy occurred in 1 and 10 cases, respectively. As shown in Figures 4 and 5, the maximum delayed bleeding rates before and after the second-look endoscopy were 2.8% and 2.5%, respectively.

DISCUSSION

Previous prospective, randomized trials revealed the efficacy of a second-look endoscopy after endoscopic hemostasis for bleeding peptic ulcers,[18-20] and this is the reason why we routinely perform a second-look endoscopy after gastric ESD. This study, however, found that

TABLE 2. Comparison of the early and late bleeding cases

	Post-ESD bleeding	
	Early (0-3 days) (16 cases)	**Late (4-14 days) (10 cases)**
Location (U/M/L)	2/4/10	4/4/2
Circumference (AW/GC/LC/PW)	2/2/7/5	3/1/4/2
Gross type (I/IIa/IIb/IIc/combined)	3/12/1	1/9/0
Ulcerative findings (presence/absence)	4/12	1/9
Resection style (en bloc/piecemeal)	15/1	9/1
Tumor size, mm (mean ± SD)	24.5 ± 19.2	19.7 ± 14.0
Tumor depth (mucosa/submucosa)	14/2	7/3
Histologic type (intestinal/diffuse/adenoma)	16/0/0	9/0/1

ESD, Endoscopic submucosal dissection; *U*, upper third; *M*, middle third; *L*, lower third; *AW*, anterior wall; *GC*, greater curve; *LC*, lesser curve; *PW*, posterior wall; *SD*, standard deviation.

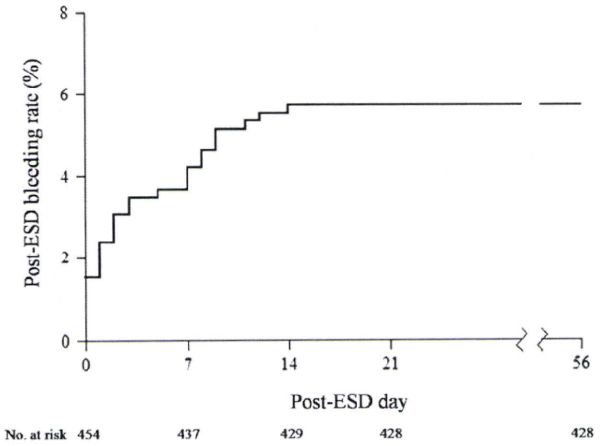

Figure 2. A post-ESD bleeding curve of all cases.

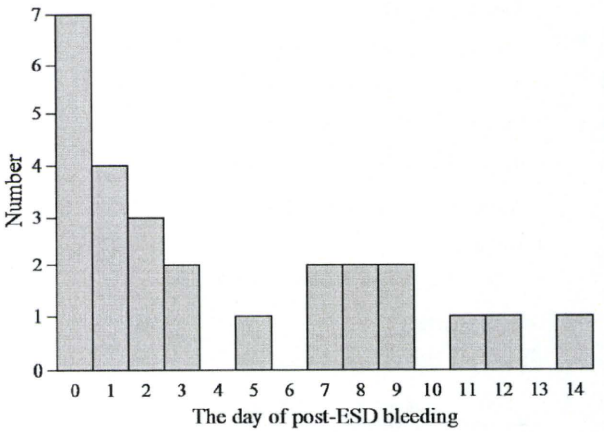

Figure 3. The post-ESD bleeding cases.

delayed bleeding occurred with similar probability between the conditions before and after a second-look endoscopy. It suggests that the second-look endoscopy may contribute less to the prevention of delayed bleeding. One of the major differences between post-ESD ulcers and peptic ulcers lies in the circumstance of ulcer formation. Peptic ulcers are usually created under low pH. Because peptic ulcers may still have the potential to bleed even after the initial hemostasis, second-look endoscopy within 24 hours may be effective.[18-20] Conversely, post-ESD ulcers are created under relatively high pH because of premedication of PPI, and are relatively similar in property so they are more easily managed without second-look endoscopy, as suggested in this study.

There is plenty of room for discussion about the use of PPIs. Intravenous administration was limited in the initial period of management, and the 3 PPIs (10 mg rabeprazole, 20 mg omeprazole, 30 mg lansoprazole twice daily) administered orally were not differentiated in our study.[16] Because there may be some differences in a variety of uses in the effect on the prevention of post-ESD bleeding,[21,22] further studies are needed to determine the optimum use of PPI, especially high-dose PPI infusion to obtain the maximum hemostatic effect.

A previous study concluded that the treatments for nonbleeding visible vessels at the final step of ESD reduced post-ESD bleeding significantly, but could not prevent it completely.[10] Furthermore, newly developing visible vessels on the ulcer bed may contribute to the bleeding in some cases. Even after treatment of visible vessels by second-look endoscopy, some cases of bleeding occurred in other locations where no vessels were seen on the second-look endoscopy, which may also suggest that a second-look endoscopy after ESD may not be useful.

In the analysis of risk factors inducing post-ESD bleeding, the flat or depressed type tumor was thought to be

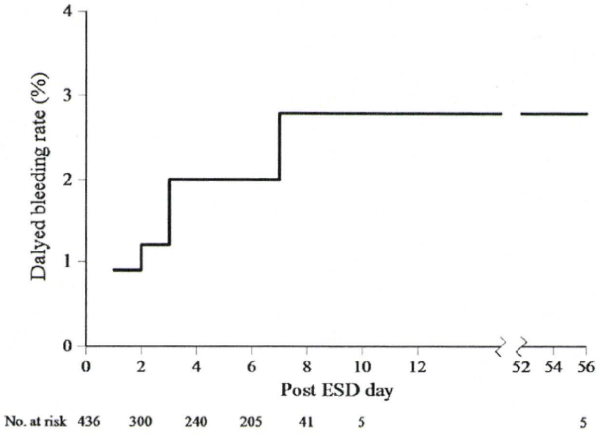

Figure 4. A curve of delayed bleeding before the second-look endoscopy. The observation period is from the day of ESD and to the second-look endoscopy. Five lesions for which the second-look endoscopy was omitted were observed for 2 months.

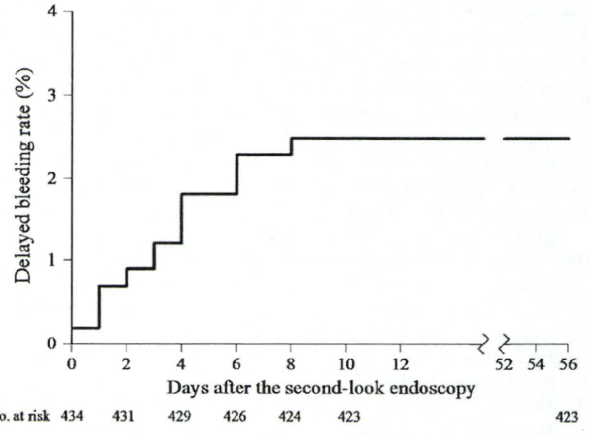

Figure 5. A curve of delayed bleeding after the second-look endoscopy. The observation period is from the second-look endoscopy to 2 months after ESD.

the predictor. The reason is not clear, but it may be because such tumors tend to be rich in vascularity. In fact, flat or depressed type tumors are mostly reddish, which indicates the existence of more vessels in the submucosal layer than in elevated type. More vessels may increase the risk of post-ESD bleeding; however, the speculation should be confirmed by further histologic study. Conversely, only 1 large case series revealed that tumor location is thought to be relevant in post-ESD bleeding and found that a tumor located in the middle or lower third of the stomach was an independent risk factor.[7] The authors speculated that the reason was that intraoperative thermocoagulation of vessels was insufficient because intraoperative bleeding was less frequent in those areas. Because careful observation of visible vessels on the mucosal defect may overcome the technical drawback, we speculate that there was no significant difference in post-ESD bleeding among the locations in this study. Further studies are needed to elucidate the risk factors of post-ESD bleeding.

This study found that post-ESD bleeding from the lower stomach lesions tends to occur earlier than that from the upper stomach. Based on the findings of this study, we may be able to change the duration of follow-up depending on the location. For example, it may be acceptable to shorten the duration of hospitalization for the patient undergoing ESD for the lesion in the lower third of the stomach.

The limitation of this study is that these analyses used retrospective data from a single center. Moreover, we could not make a pure comparison between the groups with or without the second-look endoscopy because almost all patients had been checked by the second-look endoscopy in our hospital.

In conclusion, we suggest that, although there are some differences in the possibility of delayed bleeding according to the location or gross type of the lesion, a second-look endoscopy to prevent it after ESD may be omitted to avoid an excessive or unnecessary examination. Based on these retrospective data, a prospective, randomized, controlled trial to validate second-look endoscopy should be warranted in the future.

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Received April 22, 2009. Accepted August 27, 2009.

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Digestive Endoscopy (2010) **22**, 45–48 doi:10.1111/j.1443-1661.2009.00927.x

ORIGINAL ARTICLE

FEASIBILITY OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR PATIENTS WITH CHRONIC RENAL FAILURE ON HEMODIALYSIS

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Background: Endoscopic submucosal dissection (ESD) is expected as a curative method for node-negative gastrointestinal cancers. Little is known about ESD for patients with end-stage chronic renal failure (CRF) on hemodialysis. We aimed to evaluate the efficacy and safety of ESD for patients with CRF on hemodialysis.
Methods: Ten consecutive patients with 12 lesions who underwent ESD (stomach, seven; colorectum, three) between March 2002 and August 2007 were retrospectively investigated in terms of the technical feasibility and complications.
Results: All the lesions were resected in a single piece and en-bloc and R0 resection rate was 100%. Histology revealed that all the lesions fulfilled the criteria of node-negative cancers. Delayed bleeding requiring blood transfusion on the day after ESD, and shunt occlusion, which necessitated a radiological intervention 7 days after ESD, occurred in one stomach case. Delayed perforation followed by emergency surgery 2 days after ESD occurred in one colorectal case.
Conclusions: ESD for CRF patients may be technically feasible, but substantial risks should be considered. Early detection of late-onset complications is essential with intensive medical check-up for at least 1 week in order to prevent complications from becoming severe.

Key words: chronic renal failure, endoscopic submucosal dissection, gastrointestinal cancers, hemodialysis.

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a novel, promising endoscopic technique that is expected as an alternative to open surgery for node-negative gastrointestinal cancers. It is characterized by a circumferential mucosal incision and submucosal dissection beneath the lesion, by which even a large or ulcerative lesion can be resected in an en-bloc fashion.[1] However, ESD requires highly advanced techniques to produce a safe and satisfactory resection. High rates o f complications and long procedural time are the major shortcomings of ESD,[2–4] compared to conventional endoscopic resection, namely, endoscopic mucosal resection (EMR).[5]

In general, a patient with end-stage chronic renal failure (CRF) on hemodialysis are characterized by several factors that make them poor candidates for invasive treatments (e.g. bleeding tendency, existence of cardiovascular complications, immunocompromised state, and vulnerability of tissues). From this perspective, for patients with CRF on hemodialysis, ESD should be treated as a different entity with high operative risks. However, little investigation has been carried out regarding endoscopic treatments,[6] although there have been many reports referring to outcomes of open surgery for patients with CRF.[7–9] Therefore, in this case series, we retrospectively assessed the safety and efficacy of ESD for CRF patients on hemodialysis.

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Received 28 February 2009; accepted 8 June 2009.

PATIENTS AND METHODS

From March 2002 to August 2007, 12 consecutive gastrointestinal cancers in 10 patients with CRF (nine early gastric cancers in seven patients and three colorectal cancers in three patients) were resected by ESD with a written informed consent in our hospital. Baseline characteristics of the patients are shown in Table 1. Candidates for ESD were limited to those patients that could tolerate open surgery, including an emergency operation, in case of severe complications. Those patients who had uncontrollable life-threatening diseases were excluded. All patients had a preoperative diagnosis of node-negative carcinoma or high-grade adenoma, which is defined by intramucosal or slight submucosal invasive carcinoma based on the criteria of each organ.[10,11] Diagnoses were made using chromoendoscopy, endoscopic biopsy and, occasionally, endoscopic ultrasonography or magnifying endoscopy for lesions suspected of submucosal invasion.

The ESD technique has been precisely described elsewhere.[1,10,12,13] In brief, Flex knife (KD-630L; Olympus, Tokyo, Japan) was used as the main electrosurgical knife[10,14] for circumferential mucosal cutting around the tumor with a sufficient safety margin and submucosal dissection beneath the lesion. Insulation-tipped (IT) diathermic knife (KD-610L; Olympus)[1] or Hook knife (KD-620LR; Olympus)[12] was used, depending on the circumstances. Twenty percent glucose or a mixture of 10% glycerin plus 5% fructose and 0.9% saline (Glyceol; Chugai Pharmaceutical Co., Tokyo, Japan) that contained 0.005% indigo carmine and 0.0005% epinephrine was injected into the submucosa under the lesion to make a submucosal fluid cushion.[15] Hyaluronic acid was added to the

Table 1. Baseline characteristics of 10 patients with CRF on hemodialysis who underwent endoscopic submucosal dissection

Patient	Age (years)	Sex	Cause of CRF	Duration of hemodialysis (months)	BUN (mg/dL)	Creatinine (mg/dL)	Hematocrit (%)	Prothrombin time (s)
1	66	Male	GN	30	64.1	8.90	32.7	11.2
2	60	Male	GN	61	46.3	7.86	29.6	11.8
3	62	Male	DM	21	62.1	11.13	35.9	11.3
4	66	Male	PKD	14	59.0	7.72	35.1	10.8
5	82	Male	DM	95	40.7	8.79	34.7	11.1
6	59	Female	NS	1	26.2	4.22	28.3	11.7
7	81	Male	NS	40	48.2	7.33	30.4	12.2
8	53	Male	DM	74	55.7	10.94	28.8	12.1
9	72	Male	DM	34	25.8	5.81	33.6	10.8
10	68	Male	DM	35	42.0	6.93	30.9	11.9
Median	66			34.5	47.3	7.79	31.8	11.5
(Range)	(53–82)			(1–95)	(25.8–64.1)	(4.22–11.13)	(28.3–35.9)	(10.8–12.2)

BUN, blood urea nitrogen; CRF, chronic renal failure; DM; diabetes mellitus; GN, glomerulonephritis; PKD, polycystic kidney; NS, nephrosclerosis.

injection solution for all colorectal lesions or gastric lesions with ulcerative findings or for all lesions located in a difficult area.[16] Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan) were used to control bleeding during the procedure or for ablation of visible vessels on the mucosal defect after resection.[17] In stomach cases, 5 mg diazepam and 15 mg pentazocine were initially given i.v., followed by 5 mg diazepam or 7.5 mg pentazocine, depending on the patient's condition. In colorectal cases, no sedatives or analgesics were generally used because the patient's conscious cooperation (changing position) was often needed.

In principle, preoperative hemodialysis was carried out on the day before ESD, and the patients were fasted on the day of ESD with a suitable potassium-free fluid infusion (700–1000 mL/day). On the day following ESD, hemodialysis was restarted with a light meal if the patient's symptoms, laboratory findings, and abdominal X-rays were unremarkable, and the patients were discharged when they were deemed unlikely to develop late-onset complications. A proton pump inhibitor (20 mg omeprazole i.v. bid during nil per os, followed by 10 mg/day rabeprazole, 20 mg/day omeprazole, or 30 mg/day lansoprazole orally) was given until 8 weeks after ESD,[18] and nafamostat mesilate (20–40 mg/h) instead of heparin was used as a hemodialytic anticoagulant until 1 week after ESD.[19,20] If complications occurred, the schedules were changed according to the individual patient's conditions.

In order to demonstrate the technical feasibility of ESD, en-bloc resection (one-piece resection with endoscopically lateral and basal tumor-free margins) rate, the en-bloc plus R0 resection (en-bloc with histologically lateral and basal tumor-free margins) rate, and the short-term complications occurring within 30 days after ESD were examined.

RESULTS

The outcomes of ESD are summarized in Table 2. En-bloc and en-bloc plus R0 resections were 100% and 100%, respectively. All 12 cancers were histologically diagnosed to be cured. The median duration of hospitalization was 8 days (range, 4–23 days). In one stomach case, delayed bleeding occurred on the day after ESD, and was successfully treated endoscopically. Blood transfusion was also carried out for severe anemia (minimum hemoglobin [Hb]: 5.8 g/dL), because there was pre-existing anemia due to CRF (baseline Hb: 9.0 g/dL). In this patient, shunt occlusion also occurred 7 days after ESD, which was revascularized via radiological intervention. In one colorectal case, delayed perforation occurred 2 days after ESD. In this patient, ESD was successfully finished without intraoperative perforation, but a fever greater than 38°C emerged 11 h after treatment. Conservative treatment with antibiotics and an antifebrile treatment with fasting were started immediately. Hemodialysis was carried out the following day for this patient, as originally scheduled. The patient's condition did not change for the better, and abdominal pain began 2 days after ESD. An abdominal CT scan was carried out, which showed free air with a small amount of ascites in the abdominal cavity and an inflammatory change around the lesion treated with ESD. Delayed perforation with localized peritonitis was diagnosed and emergency laparotomy (temporary colostomy with intraperitoneal drainage) was carried out 3 days after ESD. The patient was successfully treated and discharged from the hospital 23 days after ESD. During the median follow up of 27 months (range, 8–55 months), there has been no other complication or tumor-related death so far.

DISCUSSION

The present study elucidates the feasibility of ESD for patients with CRF on hemodialysis, showing a high en-bloc resection rate and en-bloc plus R0 resection rate comparable to previous reports.[2–5,10,13] It shows that the disadvantages of CRF have no influence on the procedural aspects of ESD.

The concern in this case series is greatest for complications. The major complications of ESD were delayed bleeding and perforation. In Japan, one of the leading countries for ESD, delayed bleeding rate and perforation rate were approximately 5 % each in stomach cases,[2–5] and 2% and 5% in colorectal cases.[10,13] In our hospital, delayed bleeding/perforation occurred in 4.2%/3.4% of the stomach cases and in 1.2%/4.3% of the colorectal cases between the same period. This case series, although small in number, showed no more than one complication each (one delayed bleeding in a

Table 2. Outcomes of ESD for 10 patients with chronic renal failure on hemodialysis

Patient	Organ	Location†	Gross type	Tumor size (mm)	Histological findings	Depth	En-bloc resection	En-bloc + R0 resection‡	Time (min.)	Complications
1	Stomach	M	IIc	12	Intestinal	m	Yes	Yes	60	No
2	Stomach	M	IIa	40	Intestinal	m	Yes	Yes	145	No
	Stomach	M	IIa	21	Intestinal	m	Yes	Yes	45	No
	Stomach	L	IIa	25	Intestinal	m	Yes	Yes	50	No
3	Stomach	M	IIa+IIc	30	Intestinal	m	Yes	Yes	110	No
4	Stomach	M	IIc with fibrosis	11	Intestinal	m	Yes	Yes	60	No
5	Stomach	M	IIc	7	Intestinal	sm1§	Yes	Yes	105	No
6	Stomach	L	IIc	8	Intestinal	m	Yes	Yes	35	Delayed bleeding, shunt occlusion
7	Stomach	U	IIa	17	Intestinal	m	Yes	Yes	60	No
8	Colorectum	S	LST-G-H	26	Cancer in adenoma	m	Yes	Yes	20	No
9	Colorectum	D	LST-NG-F	45	well diff. Adenocarcinoma	sm1¶	Yes	Yes	80	Delayed perforation
10	Colorectum	R	Is	18	well diff. Adenocarcinoma	sm1¶	Yes	Yes	35	No

†U, upper; M, middle; L, lower third of the stomach; S, sigmoid; D, descending colon; R, rectum.
‡En-bloc resection histologically without tumor on the edge of the resected specimen.
§Slight invasion into submucosa less than 500 μm below the muscularis mucosa.
ESD, endoscopic submucosal dissection; LST-G-H, laterally spreading tumor, granular and homogenous type; LST-NG-F, laterally spreading tumor, non-granular and flat elevated type.
¶Slight invasion into submucosa less than 1000 μm below the muscularis mucosa.

stomach case and one delayed perforation in a colorectal case). However, once a complication occurred, it tended to be more severe than in a normal case. In the case of delayed bleeding, despite successful treatments, blood transfusion was needed, although the Hb level decreased by only 3 g/dL. Without pre-existing anemia due to CRF, the blood transfusion might not have been needed. In the case of delayed perforation, an emergency surgical intervention was needed. Some causes for this were proposed. First, excessive thermal injury by submucosal dissection or hemostasis may have occurred (the procedure itself had gone smoothly and without problems, as in the other cases). Second, the large size of the mucosal defect (tumor size of 45 mm) may have led to ischemic change. Third, the vulnerability of tissues due to CRF may have induced perforation. Fourth, instability of blood flow around the treated lesion may have led to ischemic change of the mucosal defect after ESD. The patient suffered from control-resistant hypertension, especially during hemodialysis. He had also undergone laparotomy twice: sigmoidectomy for advanced colon cancer and left-nephrectomy for a renal tumor. Although we cannot know how the CRF contributed to the delayed perforation, it suggests that a patient who has several comorbidities, including CRF, should be followed more carefully even after successful treatment. For spontaneous colonic perforation, emergency surgical intervention is generally needed and, still, the mortality rate is high.[21] Therefore, early detection of delayed perforation is thought to be essential, so as not to miss the appropriate timing for surgical rescue.

In order to avoid possible complications relevant to CRF, we planned suitable perioperative schedules of ESD for the patients. First, hemodialysis was not carried out on the day of ESD because it might promote bleeding tendencies due to the use of an anticoagulant. Second, we selected nafamostat mesilate as the anticoagulant during hemodialysis carried out around the time of operation.[19,20] This ultra-short-acting multi-enzyme inhibitor is thought to reduce the risk of bleeding, but it has not been a standard drug except in Japan due to a lack of consensus about its efficacy. Third, infusion solutions were cautiously selected to avoid electrolyte imbalance and hemodynamic instability. In this case series, hyperkalemia or cardiopulmonary dysfunction, the major complications of surgery for CRF patients,[7–9] were not seen.

Although there are many obstacles to carrying out ESD on patients with CRF, we still recommend that ESD should be the first choice for curatively resectable tumors, because it is evident that endoluminal surgery is less invasive than open surgery. Factors associated with CRF affect operative risks equally, whether ESD or open surgery. Therefore, the choice of less invasive surgery is quite acceptable, if the same efficacy and precariousness exist. However, a less invasive treatment method than ESD, as EMR is thought to be, may be advantageous, but curative resection may not be as likely with EMR, especially for large tumors. In addition, the resection of a recurrent tumor after incomplete EMR is thought to be more difficult and risky.

A limitation of the present study is that it was a retrospective, single-center, small-sample analysis. Moreover, long-term validity has not been investigated in the present study because of a relatively short observation period. An accumulation of cases with long-term analysis is needed for a confirmation of the safety and efficacy of ESD for CRF patients.

In summary, we confirmed the short-term feasibility of ESD for CRF patients. However, complications may turn out to be severe, so early detection of complications with intensive check-up after ESD for at least 1 week is thought to be essential.

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Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms

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submitted 20 February 2010
accepted after revision
16 June 2010

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DOI http://dx.doi.org/10.1055/s-0030-1255675
Endoscopy 2010; 42: 723–729 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

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Background and aims: Endoscopic submucosal dissection (ESD) provides a high en bloc resection rate with less invasiveness than surgical resection for large or scarring gastrointestinal neoplasms. However, detailed outcomes in colorectal ESD are still lacking. The aim of our study was to elucidate short- and long-term outcomes of colorectal ESD.

Patients and methods: 310 consecutive colorectal epithelial neoplasms (146 adenomas, 164 carcinomas), in 290 patients, which fulfilled our indication criteria and were treated with ESD between July 2000 and December 2008 were studied. ESD was done by three skilled endoscopists. As short-term outcomes, rates of en bloc resection, en bloc plus R0 resection, and major complications were analyzed. As long-term outcomes, disease-free and overall survival were assessed in 224 patients.

Results: Rates of en bloc resection and en bloc plus R0 resection were 90.3% and 74.5%, respectively. Eight patients underwent additional colectomy due to histopathologically proven possible node-positive cancer. Intraoperative perforations occurred with 14 lesions (4.5%), which were treated successfully only by endoscopic clipping. Emergent surgery was needed for one case of postoperative perforation. Blood transfusion due to intraoperative massive bleeding was required in 1 case (0.3%). Postoperative bleeding occurred with four lesions (1.3%), and was endoscopically managed without blood transfusion. Local recurrence was detected in 4 lesions (4/202 patients, 2.0%); resection had been piecemeal in all 4. During a median follow-up of 38.7 months (range 12.8–104.2), the 3- and 5-year overall/disease-specific survivals were 97.1/100% and 95.3/100%, respectively.

Conclusions: Colorectal ESD showed favorable long-term outcomes. It may largely replace colectomy for node-negative colorectal epithelial neoplasia.

Introduction

Endoscopic submucosal dissection (ESD) for stomach epithelial neoplasms has gained acceptance as a standard treatment for node-negative tumors in advanced countries [1,2]. This success argues for application of this promising technique in the colorectum, because only lesions less than 20 mm are suitable for en bloc endoscopic mucosal resection (EMR) and lesions cannot be resected by EMR if they have submucosal fibrosis due to intensive biopsy or previous unsuccessful attempts at endoscopic removal [3].

However, the anatomical and histological differences from the stomach must be considered in order to apply the ESD technique in the colorectum. Its tortuous structure and thinner wall lead to a higher likelihood of complications such as perforation. Additionally, if perforation occurs, the entry of feces and bacteria into the peritoneum would easily cause panperitonitis. So complete mastery of the technique is necessary. Three other requirements are demanded for colorectal ESD: first, intensive lavage throughout the colorectum; second, a safer electrosurgical knife; and, third, a long-lasting submucosal fluid cushion. After these implementing these refinements of the stomach ESD technique, we began to carry out colorectal ESD from July 2000.

We have previously described promising short-term outcomes of colorectal ESD [15], but the long-term outcomes have not been reported. In the present study, we retrospectively assessed the long-term outcomes of ESD for colorectal epithelial neoplasms from an increased number of our consecutive cases with a longer median duration of follow-up.

Patients and methods

Between July 2000 and December 2008, 290 consecutive patients, who had a total of 310 colorectal epithelial neoplasms, were treated by ESD at the University of Tokyo Hospital in Tokyo, Japan. All patients were informed about the risks and benefits of several treatment options, including ESD, conventional EMR, ablation therapy, and conventional surgery, and provided written informed consent to ESD treatment. This study was approved by the ethics committee of our institute.

ESD treatment was done by three endoscopic specialists who had certification from the Japan Gastroenterological Endoscopy Society and who were highly experienced in performing stomach ESD. The indication for ESD was determined by endoscopic features, seen using chromoendoscopy, and occasionally magnifying endoscopy or endoscopic ultrasonography (EUS). EUS was used for the special cases of scarring lesions or when magnifying endoscopy raised the suspicion of massive submucosal invasion. Biopsy was not necessary to determine the indication because prediction of neoplasm was completely determined by chromoendoscopy; biopsy might cause submucosal fibrosis which would make subsequent endoscopic resection more risky and difficult.

The indication for ESD at our center was colorectal epithelial neoplasia which might have a malignant component with a prediction of node-negative tumors, and/or that posed technical difficulty in terms of complete removal by other endoscopic resection methods, for example, because of submucosal fibrosis. However, some lesions with an associated prediction of possible node-positive carcinomas, were locally resected by ESD because of the patient's wish or to obtain an accurate histological diagnosis, when the operator judged the lesions were technically resectable by ESD.

The endoscopic characteristics of the tumors were categorized according to our modification of the Paris endoscopic classification [4]. Histological assessment was described according to the revised Vienna classification of gastrointestinal epithelial neoplasia. Macroscopically the indicated tumors were classified using four types: protruding large tumor (type 0-I); laterally spreading tumors (LSTs) with four subtypes according to Kudo's classification (granular and homogeneous [LST-GH]), granular and nodular mixed [LST-GM], nongranular and flat elevated [LST-NGF], and nongranular and pseudodepressed [LST-NGPD]; intraepithelial tumor with submucosal fibrosis showing the nonlifting sign, because of previous endoscopic treatment or biopsy (scar type); or depressed tumors (type 0-IIc or 0-IIa + IIc). The tumor morphologies (LST subgroups, depressed-type, and scarring tumor) were re-evaluated carefully for this study with discussion between three experienced endoscopists (N.Y., S.K., M.F.) referring to the patients' reports and the endoscopic photos during ESD.

Technical details of colorectal ESD

The ESD procedure was performed as previously described elsewhere [9,15]. The bowel was prepared by means of a low-fiber diet the day before ESD, 10 ml of 0.75% sodium picosulfate solution (Laxoberon; Teijin Pharma, Tokyo, Japan) the night before ESD, and 10 mg of mosapride citrate (Gasmotin; Dainippon Sumitomo Pharma, Osaka, Japan) and 2L of an isotonic polyethylene glycol electrolyte solution (Niflec; Ajinomoto Pharma, Tokyo, Japan) on the morning of ESD.

ESD was generally done using a single-channel upper gastrointestinal endoscope with a water-jet system (GIF-Q260J, Olympus Medical Systems, Tokyo, Japan; or EG-2931, Pentax Hoya, Tokyo, Japan). In the case of tumors located in the proximal colon that were not reachable by the upper gastrointestinal endoscope, a slim colonoscope with or without a water-jet system (PCF-Q260JI or PCF-P240AI; Olympus) was used. The electrosurgical unit used was the ICC 200 (Erbe Elektromedizin, Tübingen, Germany) from July 2000 to March 2005, or the VIO 300D (Erbe Elektromedizin) from April 2005. A transparent hood was attached to the tip of the endoscope to provide a constant endoscopic view and to apply countertraction to the connective tissue for submucosal dissection. For submucosal injection, a mixture of a 1% 1900-kD hyaluronic acid preparation (Suvenyl; Chugai Pharmaceutical, Tokyo, Japan) plus normal saline was used from July 2000 to October 2003, and 10% glycerin plus 5% fructose and 0.9% saline preparation (Glyceol; Chugai Pharmaceutical) was used from November 2003 to March 2008. From April 2008, a 0.4% hyaluronic acid preparation (Mucoup; Johnson & Johnson, Tokyo, Japan) was used as the substitute, because this preparation went on the market in Japan as a medical material specifically for submucosal injection. To clarify the injection area and to distinguish clearly between the muscle and submucosal layers, indigo carmine was added to the solution at concentrations of 0.005%. As an electrosurgical knife we mainly used the tip of the thin type SD-7p-1 electrosurgical snare (Olympus) from July 2000 to October 2002, or the Flex knife (KD-630L; Olympus) from November 2002). In situations where dissection was difficult we used the Hook knife (KD-620LR; Olympus) in combination with the Flex knife. Hemostatic forceps (SDB2422; Pentax Hoya) were used to control any visible bleeding. ESD was generally performed without sedation. After the completion of ESD, the patient stayed in bed until the next morning, and if the patient's condition, the laboratory data, and abdominal X-ray revealed no significant abnormality, a soft diet was begun. Patients were discharged from the ward several days after ESD. If there were complications, the clinical approach after ESD was dependent on the patient's situation.

Histopathological evaluations and follow-up

Resected margins of the obtained specimens were assessed as complete resection (R0), incomplete resection (R1), or not evaluable (Rx), according to the lateral and basal extension of tumor cells. Lesions without a tumor-free lateral margin (R1 or Rx [lateral] resection) were generally observed carefully every 3–6 months by follow-up colonoscopy without additional treatment because the burn effects on the resected tissue sometimes made it difficult to evaluate the lateral margins precisely. In the case of a histological diagnosis of possible node-positive tumor, patients were usually sent for surgery for additional colorectal resection with lymph node dissection. The remaining patients were followed without additional treatment, with follow-up colonoscopy usually performed about 2 months after ESD to confirm healing of the post-procedure ulcers and to check for the presence of residual tumor, and annually thereafter to check for local recurrence and/or second primary tumors. The existence of distant or lymph node metastasis in patients with noninvasive carcinoma was indefinitely evaluated through medical check-ups, including computed tomography (CT) and measurement of serum CEA level. In the case of invasive carcinoma, the patients were generally followed by CT and serum CEA measurement every 6 months.

In order to analyze the long-term outcomes, a questionnaire was sent to 198 patients who had no follow-up medical records at the end of December 2008. The following information was request-

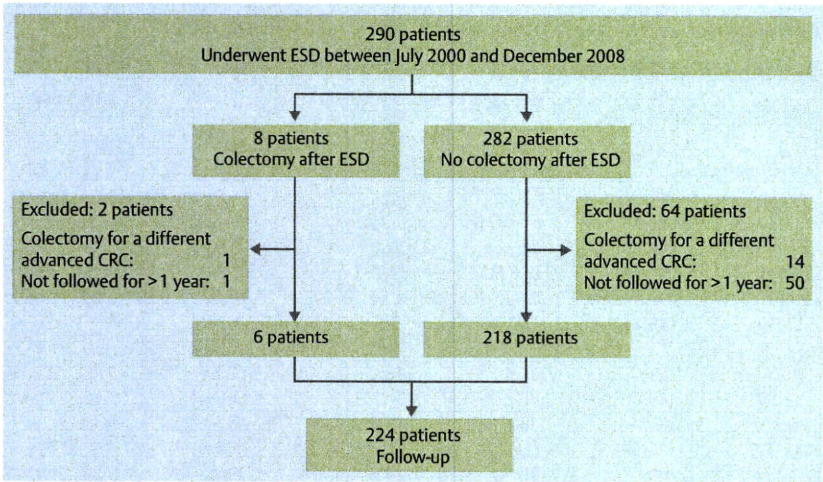

Fig. 1 Inclusion of patients in analysis to evaluate long-term outcomes of endoscopic submucosal dissection (ESD) for colorectal neoplasia. CRC, colorectal cancer.

ed: date of latest endoscopy; date of latest CT; and whether there had been local recurrence, second primary tumor, or metastasis. A total of 123 patients (62.2%) had responded to our questionnaire by the end of March 2009.

The parameters assessed in this study were the rates of en bloc resection, en bloc plus R0 resection, major complications, and overall and disease-free survival after ESD. To evaluate the long-term survival outcomes, 224 patients who were followed over 1 year and had not undergone colectomy for another different advanced colorectal cancer were included in the analysis (**Fig. 1**), and the observation period was from the date of ESD to the date when survival was confirmed.

To evaluate the long-term outcomes for local recurrence, 202 patients who had undergone colonoscopy one or more times after ESD were included in the analysis, with an observation period from the date of ESD to the date of the last colonoscopy.

Statistical analysis

Statistical analysis for survival was done using the Kaplan-Meier method and the log rank test. *P* values of less than 0.05 were considered significant. All statistical analyses were carried out using JMP version 8 software.

Results

Colorectal epithelial neoplasms treated by ESD

Table 1 summarizes the clinicopathological features of 310 colorectal epithelial neoplasms treated by ESD. A total of 53 neoplasms (17.1%) were histopathologically revealed to be invasive carcinoma, and one could not be classified because of the burn effect on the resected tissue.

Further treatment was done on the basis of a histological diagnosis of sm2 or deeper invasion and/or vessel infiltration by cancer cells [5]. A total of 18 carcinomas (5.8% of lesions) in 18 patients were considered to be at substantial risk for nodal metastasis; these comprised 16 carcinomas with sm2 or deeper invasion, which included 5 carcinomas with vessel infiltration, and 2 carcinomas with sm1 invasion and vessel infiltration.

Among these 18 patients, 8 additionally underwent colorectal resection with lymphadenectomy. In these patients (6 men, 2 women; median age 61.3, range 54–73), the size of lesions ranged from 18 to 100 mm with a median size of 38.1 mm; the lesion locations were cecum (n = 1), sigmoid colon (n = 4), and rectum (n = 3). Residual carcinoma was found in the resected colon wall in 2 patients and in lymph nodes in 2 patients. The remaining 10 patients with possible node-positive tumors were followed without additional treatment either because the patients refused further treatment or the operation was very risky

Table 1 Patient characteristics (n = 290) and clinicopathological features of 310 colorectal epithelial neoplasms treated with endoscopic submucosal dissection (ESD).

Patients	
Age, mean (range), years	65.3 (29–88)
Sex, men, women	94,196
Lesions	
Size, mean (range), mm	28.9 (6–100)
Location, n	
Cecum	27
Ascending colon	57
Transverse colon	61
Descending colon	21
Sigmoid colon	63
Rectum	81
Macroscopic tumor type, n	
0-I protruding	35
Laterally spreading tumors (LSTs)	
Granular and homogeneous (GH)	57
Granular and mixed (GM)	86
Nongranular and flat elevated type (NGF)	77
Nongranular and pseudodepressed (NGPD)	25
Scar*	24
0-IIc, 0-IIa + IIc, depressed	6
Histological depth†, n	
Low-grade adenoma	61
High-grade adenoma	85
Noninvasive carcinoma	110
sm1	37
sm2 or deeper	16
Unclassified	1
Vessel infiltration, n	
Present	9
Absent	301

*Scar, tumor showing nonlifting sign because of submucosal fibrosis caused by previous endoscopic treatment or biopsy.

† The cutoff between sm1 and sm2 is 1000 µm; sm1, minimally invasive carcinoma with infiltration depth ≤ 1000 µm; sm2, massive invasive carcinoma with massive submucosal invasion > 1000 µm below the muscularis mucosa.

Table 2 Features according to macroscopic type of 310 colorectal epithelial neoplasms treated with endoscopic submucosal dissection (ESD).

	0-I	Laterally spreading tumors (LSTs)				Scar	0-IIc or 0-IIa + IIc
		LST-GH	LST-GM	LST-NGF	LST-NGPD		
Mean size mm	27.5	32.1	38.8	21.8	19.8	22.1	16.7
Location, % (n/n)							
Proximal colon*	22.9 (8/35)	57.9 (33/57)	36.0 (31/86)	53.2 (41/77)	68.0 (17/25)	45.9 (11/24)	33.3 (2/6)
Distal colon†	31.4 (11/35)	12.3 (7/57)	22.1 (19/86)	40.3 (31/77)	32.0 (8/25)	33.3 (8/24)	33.3 (2/6)
Rectum	45.7 (16/35)	29.8 (17/57)	41.9 (36/86)	6.5 (5/77)	0	20.8 (5/24)	33.3 (2/6)
Histological depth, % (n/n)							
Low-grade adenoma	14.3 (5/35)	31.6 (18/57)	9.3 (8/86)	26.0 (20/77)	16.0 (4/25)	29.2 (7/24)	0
High-grade adenoma	17.1 (6/35)	26.3 (15/57)	30.2 (26/86)	33.8 (26/77)	12.0 (3/25)	33.3 (8/24)	0
Noninvasive carcinoma	34.3 (12/35)	42.1 (24/57)	41.9 (36/86)	29.9 (23/77)	24.0 (6/25)	29.2 (7/24)	33.3 (2/6)
sm1	22.9 (8/35)	0	13.9 (12/86)	6.5 (5/77)	44.0 (11/25)	8.3 (2/24)	0
sm2 or deeper	11.4 (4/35)	0	4.7 (4/86)	2.6 (2/77)	4.0 (1/25)	0	66.7 (4/6)
Unclassified	0	0	0	1.3 (1/77)	0	0	0

0-I, protruding large tumor; LST-GH, granular and homogeneous; LST-GM, granular and nodular mixed; LST-NGF, nongranular and flat elevated; LST-NGPD, nongranular and pseudodepressed; Scar; intraepithelial tumor with submucosal fibrosis showing the nonlifting sign, because of previous endoscopic treatment or biopsy; 0-IIc or 0-IIa + IIc, depressed tumor.

*Proximal colon: cecum, ascending colon, and transverse colon.

†Distal colon: descending colon and sigmoid colon.

for them. These patients survived without cancer recurrence for a median follow-up of 22 months (range 4–48 months).

Table 2 shows the analysis of the lesions according to macroscopic type. Although all of the LST-GH tumors were intramucosal, nearly half of the LST-NGPD tumors (48.0%) showed submucosal invasion. It is also seen that type 0-I and LST-GM tumors were predominantly found in the rectum, while the other tumor types were found predominantly in the proximal colon.

Short-term outcomes

The short-term outcomes of colorectal ESD according to macroscopic type of the neoplasm are shown in **Table 3**. Overall rates of en bloc resection and en bloc plus R0 resection were 90.3% (280/310) and 74.5% (213/310), respectively. Overall R1 resection rates were lateral 12.6% (39/310) and basal 1.3% (4/310). Overall Rx resection rates were lateral 11.3% (35/310), and basal 0.3% (1/310).

Perforation occurred with 15 lesions (4.8%). Intraoperative perforation occurred in 14 lesions (4.5%); of these, three were perforations with no air leak, that were not detected by postoperative X-ray, and three were penetrations. They were managed with conservative medical treatment after endoscopic closure of the perforation and got better without additional surgery. For one lesion (0.3%) there was postoperative perforation 2 days after the ESD, which was treated by laparotomy. The patient involved had several comorbidities including hypertension, diabetes mellitus, post-sigmoidectomy and post-left nephrectomy status, and was on hemodialysis for chronic renal failure. The lesion was an LST-NGF sm1 carcinoma, 4 cm in size, and located in the descending colon. ESD had been successfully completed without intraoperative complications and free air had not been detected at X-ray the day after ESD; however fever and abdominal pain occurred 2 days after ESD and the diagnosis of perforation was made by means of a CT scan.

Minor bleeding was encountered in all resections, but hemostasis was achieved during the procedures. Blood transfusion due to massive intraoperative bleeding was required in one case (0.3%). The lesion involved was an LST-GM type with a large nodule, 4 cm in size, and located in the sigmoid colon; it was supposed to be invading the submucosa. Spurting bleeding occurred after the final step of resection with a snare. Four resections (1.3%) required emergency colonoscopies as a result of hematochezia after ESD, in order to apply endoclips for the causal vessels on the postoperative ulcers. All lesions were treated only by endoscopic clipping. In two patients the lesions were located in the rectum and clipping was required within 24 hours and 10 days after ESD, respectively; in one patient the lesion was in the ascending colon, with clipping 2 days after ESD; and finally in one patient the lesion was in the cecum and clipping was done 4 days after ESD. All of the bleeding lesions were LST-GM types.

Long-term outcomes

Local recurrence. The median duration between ESD and the last colonoscopy was 30.6 months (range, 0.6–97.1). Local recurrence was detected in four patients (2/202 patients; 2.0%); in all four cases the resections had been piecemeal. The first patient had an LST-GM noninvasive carcinoma in high-grade adenoma, 5 cm in size, and located in the lower rectum, which was resected in seven pieces with an R1 (lateral) resection. The second patient had an LST-GM sm1 recurrent carcinoma after repeated EMR, 3 cm in size, and located in the transverse colon; this was resected in three pieces with an Rx (lateral) resection. In the third patient, the lesion involved was an LST-NG noninvasive carcinoma, with scar, 3 cm in size, and in the transverse colon; this was resected in four pieces with an Rx (lateral) resection. This lesion

Table 3 Technical outcomes, according to lesion macroscopic type, endoscopic submucosal dissection (ESD) of 310 colorectal epithelial neoplasms.

	0-I	Laterally spreading tumors (LSTs)				Scar	0-IIc or 0-IIa + IIc	Total
		LST-GH	LST-GM	LST-NGF	LST-NGPD			
En bloc resection, % (n/n)	91.4 (32/35)	89.5 (51/57)	94.2 (81/86)	94.8 (73/77)	80.0 (20/25)	79.2 (19/24)	83.3 (5/6)	90.3 (280/310)
Resection status, % (n/n)								
R0 (complete)	80.0 (28/35)	77.2 (44/57)	76.7 (66/86)	74.0 (57/77)	64.0 (16/25)	62.5 (15/24)	83.3 (5/6)	74.5 (231/310)
R1 (lateral)*	5.7 (2/35)	14.1 (8/57)	15.1 (13/86)	14.3 (11/77)	8.0 (2/25)	12.5 (3/24)	0	12.6 (39/310)
R1 (basal)†	0 (0/35)	0	1.2 (1/86)	1.3 (1/77)	4.0 (1/25)	4.2 (1/24)	0	1.3 (4/310)
Rx (lateral)‡	14.3 (5/35)	7.0 (4/57)	7.0 (6/86)	10.4 (8/77)	24.0 (6/25)	20.8 (5/24)	16.7 (1/6)	11.3 (35/310)
Rx (basal)‡	0	1.7 (1/57)	0	0	0	0	0	0.3 (1/310)
Complications, % (n/n)								
Perforation	2.6 (1/35)	7.0 (4/57)	7.0 (6/86)	1.3 (1/77)	0	12.5 (3/24)	0	4.8 (15/310)
Bleeding	0	0	5.8 (5/86)	0	0	0	0	1.6 (5/310)

0-I, protruding large tumor; LST-GH, granular and homogeneous; LST-GM, granular and nodular mixed; LST-NGF, nongranular and flat elevated; LST-NGPD, nongranular and pseudodepressed; Scar; intraepithelial tumor with submucosal fibrosis showing the nonlifting sign, because of previous endoscopic treatment or biopsy; 0-IIc or 0-IIa + IIc, depressed tumor.

*Tumor extending to lateral margins.

†Tumor extending to basal margins.

‡Margins not evaluated.

was located in a tortuous area and there were breathing fluctuations and occasional severe peristalsis which caused penetration during ESD. The fourth case of local recurrence was associated with an LST-GM noninvasive carcinoma, in high-grade adenoma, 10 cm in size, located in the rectum, which had been resected in eight pieces with an Rx (lateral) resection. The patient had a vaginal ring which had been inserted for prolapse of the uterus, and the ring was piercing the upper rectum. During ESD, shivering due to possible bacteremia from the piercing ring occurred, which required the procedure to be completed quickly; this improved with antibiotic treatment.

The second patient was treated by additional surgery 2 years after ESD, and the other recurrences were managed with further endoscopic treatment.

The local recurrence rate was significantly different for lesions with and without en bloc resection, at 0% (0/182) vs. 20% (4/20) ($P=0.01$). All the other patients showed no evidence of distant recurrence when medical checkups had been performed.

Survival. The median follow-up observation was 38.7 months (range 12.8–104.2). The 3-year overall/disease-specific survival was 97.1%/100% and the corresponding 5-year values were 95.3%/100% (**Fig. 2**). Eight patients died of other coexisting disease. No patient died of colorectal cancer.

Discussion

This clinical study clearly demonstrated the efficacy and acceptable safety of colorectal ESD over our 8-year experience. It has been considered that ESD is probably a feasible technique for treating large or scarring superficial colorectal neoplasms, because previous studies from several investigators concerning colorectal ESD have also shown favorable short-term outcomes [6–14]. However, it has not yet been established as a standard therapeutic method, because of the possible complication risks and the lack of data concerning long-term outcomes.

The risks of complication mainly arise from organ-specific characteristics: the thinner wall, stronger peristalsis, and the tortuous anatomy. It is sometimes difficult to maneuver the scope; handling is quite different from that in the upper gastrointestinal tract. In comparison with our preliminary study for colorectal ESD [15, 16], however, the rate of complications tended to be lower in the present study. This suggests that the complications are preventable with experience and with technical advances and innovation in the performance of colorectal ESD, similarly to the learning curve for stomach ESD [17].

With regard to a learning process for colorectal ESD, Japanese endoscopists or those in other countries with a high incidence of gastric cancer can start by performing ESD in the stomach, as we did. However, endoscopists in countries with low incidence, especially Western countries, have to begin with colorectal procedures to acquire proficiency in ESD techniques. Our recommendation in such cases is that, after learning how to perform ESD in animal training models, operators should start with smaller LSTs in the rectum; this is fairly straight and stable within the pelvis and offers a wide working space. Then a gradual progression, for example from the rectum to the distal colon and from smaller LSTs to larger LSTs, is essential for the successful introduction of colorectal ESD in those countries with low gastric cancer incidence..

This study implies that macroscopic type affects the probability of complications, although statistical analysis was not conducted because the number of cases was small. All bleeding complications occurred with LST-GM lesions. The reason is unclear; it is possible that LST-GMs have a thick blood vessel or are well-vascularized under the large tumor nodule. Regarding perforation, ESD for scarring lesions tended to show a higher risk than for other lesions. This might be linked with missing the level of submucosal dissection in the fibrotic tissue. The presence of fibrosis

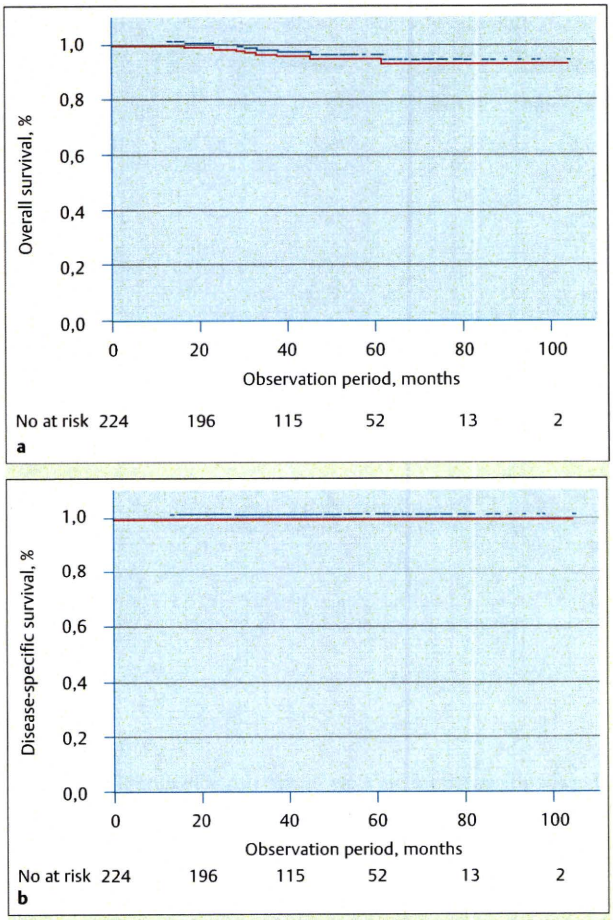

Fig. 2 Kaplan-Meier estimates of survival in patients who underwent endoscopic submucosal dissection (ESD) for colorectal neoplasia: **a** overall survival; **b** disease-specific survival.

requires high levels of endoscopic skills and experience. This hypothesis is supported by one recent study concerning colorectal ESD, which revealed that the presence of fibrosis and larger tumor size (≥ 3 cm) were significant risks for perforation [8].

With regard to en bloc resection rates, this study revealed lower rates, around 80%, for LST-NGPDs, scarring tumors and depressed tumors, in comparison with those in the other subgroups, of around 90%. It is known that submucosal fibrosis occurs most often in tumors in these three subgroups. Furthermore, the LST-NGPD tumors were predominantly located in the proximal colon. A previous study from another group has also shown that that right-side colon location and fibrosis are significant risks for incomplete resection [8], which is also supported by our present study.

This study is the first report showing the long-term outcomes of ESD for colorectal epithelial neoplasms. During a median follow-up of approximately 3 years, the disease-specific survival was 100% and no distant metastasis was observed. The only problem might be local recurrence. However, the 2.0% local recurrence rate was notably lower than that found with piecemeal EMR when the mean size of target lesions was around 3 cm [18]. Additionally, this study revealed that all the local recurrences were observed in patients with piecemeal resection. Thus, careful observation of these patients was essential during follow-up colonoscopies after ESD. However, further intensive follow-up colonoscopies seem unnecessary, because from the beginning all but one sm tumor could be managed by additional endoscopic treatment in our study. Additional endoscopic treatment for residual or locally recurrent tumor was also considered to be acceptable in a report from another group using ESD [19].

We recognize that the limitations of this study are its retrospective design, single-center analysis, lack of comparison with another modality, and, to some extent, recall bias. We believe that we performed ESD for the lesions for which ESD was appropriate; otherwise surgery was conducted. However, we have no data showing the survival benefits of endoscopic treatment over surgery. Furthermore, there is no prospective comparative study concerning ESD and piecemeal EMR. To obtain high-quality evidence on the benefit of ESD, we must wait for a large number of prospective, multicenter comparative studies.

In conclusion, colorectal ESD showed favorable long-term outcomes. The complications seem to be decreasing gradually with our progress along a learning curve. However, larger size of tumor, right-sided colon location, and presence of fibrosis are contributing risk factors for complication and incomplete resection. Benefits and underlying risks might vary, depending on the tumor characteristics and the endoscopist's technical skills. Therefore, it is desirable at present that only skilled and experienced endoscopists should treat such high risk lesions. Further improvements in colorectal ESD appear to be necessary, and this modality may replace colectomy for most node-negative colorectal epithelial neoplasms in the near future.

Competing interests: None

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