Predictive factors for complications in endoscopic resection of large colorectal lesions: a multicenter prospective study
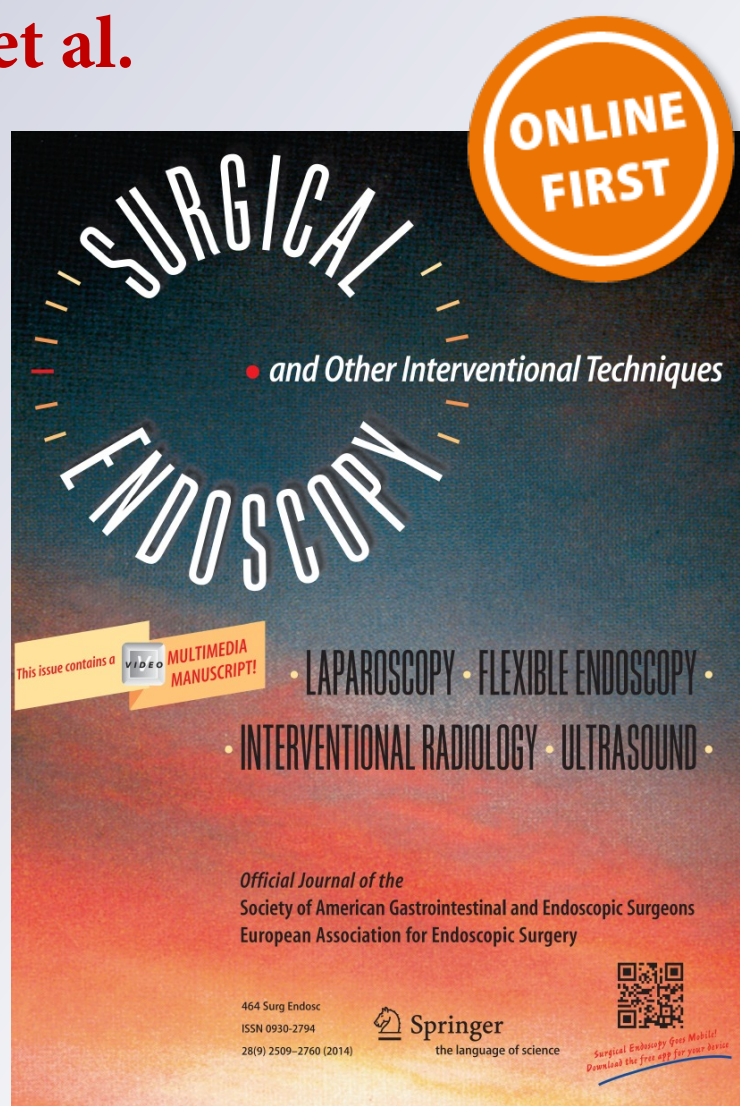
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Abstract

Background and study aims Conventional endoscopic resection (CER) includes polypectomy and endoscopic mucosal resection. The most common complications related to these techniques are post procedure bleeding and perforation. The aim of this study was to evaluate the outcomes of CER for colorectal neoplasms ≥ 20 mm and to clarify predictive factors for complications.

Patients and methods We conducted a multicenter prospective study at 18 specialized institutes. From October 2007 to December 2010, 1,029 CERs were performed at participating institutes. We collected the data prospectively and analyzed gender, age, tumor size, gross appearance, mode of resection, etc.

Results The mean size of polyps resected was 26.4 ± 8.6 mm (range 20–120 mm). The final pathology was Vienna classification category 1 or 2 in 24, category 3 in 502, and category 4 or 5 in 503 lesions. Post procedure bleeding and intra procedure perforation occurred, respectively, in 16 (1.6 %) and 8 cases (0.78 %). The overall complication rate was 2.3 %. Risk factors for bleeding in multivariate analysis were only patients under 60 years of age. Risk factors for perforation in multivariate analysis were en bloc resection and Vienna classification category 4–5. The difference of complication rate was not statistically significant regarding gender, size, tumor location, gross appearance, treatment method, and kind of insufflation.

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Conclusion CER is a safe, efficient, and effective minimally invasive therapy for large colorectal lesions. However, care should be taken for post procedure bleeding in patients under 60 years of age and for perforation in cases of Vienna classification category 4–5 or when an en bloc resection is tried.

Keywords Conventional endoscopic resection · Post procedure bleeding · Perforation · Large colorectal lesion

Endoscopic resection is a preferred method of treating majority of polyps and some of early cancers in the colorectum. Large sessile and flat colonic lesions have been found in 0.8–5.2 % of patients undergoing colonoscopy for different indications [1]. These lesions represent a therapeutic challenge because they are associated with higher incidence of high-grade dysplasia or adenocarcinoma and complication such as post procedure bleeding or perforation [2].

Polypectomy technique is useful for pedunculated lesions, whereas endoscopic mucosal resection (EMR) is necessary to treat sessile or non-polypoid colorectal lesions. The latter procedure consists of two steps: 1. expanding the submucosal layer away from the muscularis propria by injection of solution and 2. resecting between these layers to effectively remove the lesion [3, 4]. Colorectal lesions without risk of lymph node metastasis are good candidates for endoscopic resection [5]. Both polypectomy and EMR techniques are widely accepted as minimally invasive treatment for colorectal neoplasia. In this study endoscopic resection using a snare, including both of polypectomy and EMR, was defined as conventional endoscopic resection (CER).

Endoscopic submucosal dissection (ESD) is an established therapeutic technique for the treatment of gastric neoplasms. It enables en bloc resection and, therefore, provides an ideal specimen for precise histopathological evaluation [6, 7]. However, colorectal ESD is demanding and carries a higher risk of perforation because the colonic wall is thinner and stabilization of an endoscope is more difficult than in gastric or esophageal ESD [8, 9]. Therefore, colorectal ESD is still not a globally accepted procedure. Meanwhile, CER for large colorectal neoplasia has been widely spread as a safe and effective method. The main complications associated with CER are post procedure bleeding and perforation. Despite the numerous number of publications on case series of CER for larger polyps, risk factors for complications have not been comprehensively analyzed yet except for only a few literature [10, 11].

Materials and methods

We conducted a multicenter prospective study in cooperation with Japanese Society for Cancer of the Colon and Rectum (JSCCR) in order to clarify predictive factors for complications associated with CER. The study was carried out at 18 institutions from all over Japan which include high- and medium-volume centers with various levels of experience. The present study was designed as an exploratory analysis to investigate the outcomes of colorectal CER and predictive factors for complications associating the procedure. The data analyzed in this observational study were obtained from a prospective multicenter cohort trial conducted by JSCCR. The main endpoint of the latter was to compare the recurrence rate after endoscopic resection for colorectal neoplasms sized 20 mm or larger between en bloc resection and piecemeal resection. The primary results of the prospective cohort trial will be disclosed in the future. The study protocol of the cohort study was approved by the institutional review board at each center and registered in the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (registration number: UMIN 000001642).

Sample size of the original cohort study was calculated based on the recurrence rate after endoscopic resection in previous reports. This was a non-randomized cohort trial. It was assumed that the recurrent incidence after en bloc resection and piecemeal resection would be different. We hypothesized that the recurrence rate after piecemeal resection would be 5 % higher than after en bloc resection which had been reported to be around 5 %. Power analysis indicated that more than 500 lesions were required for each group (en bloc resection vs. piecemeal resection) to achieve 5 % significance level and statistical power of 80 % using a two-sided equivalence.

From October 2007 to December 2010, consecutive patients with colorectal lesions sized 20 mm or larger were prospectively enrolled at the 18 institutions. The size of each lesion was determined endoscopically, compared with the diameter of the snare. All the data obtained were sent to a data center, which is independent from any participating institute. The study was conducted with the approval of each institution's ethical review board, and written informed consent was obtained from all the patients. In order to avoid bias, the patient was enrolled before the treatment and all the data were collected after the procedure.

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All procedures were performed by experienced colonoscopists, or under their supervision. Endoscopic therapeutic method (CER or ESD) for each lesion was selected by each colonoscopist based on his or her experience. Selection for scopes, devices, lifting solutions, or premedications was not regulated by the study protocol and all the procedures were performed according to each institute's preference.

As previously described, endoscopic resection using a snare, including both polypectomy and EMR, was defined as CER in this study. Polypectomy can be defined as resection of protruded lesion, mainly pedunculated, without injection of solution. To choose polypectomy technique or EMR was decided by the operating endoscopist according to the size and gross appearance of the lesion. Indications for EMR included sessile or flat adenomas and early cancers without apparent deep submucosal invasion. Piecemeal resection was performed as needed. If there was a suspicion of small residue after the snare resection, coagulation using hot biopsy forceps or argon plasma was applied.

Complications were prospectively collected by the close observation of the patient during hospitalization and by the interview of patients at the outpatient clinic 2–4 weeks after the procedure. Post procedure bleeding was suspected when the patient complained rectal bleeding. Post procedure bleeding in this study was defined as bleeding after leaving the endoscopic room which was associated with decrease of hemoglobin >2 g/dl, requirement for blood transfusion or a repeat colonoscopy for hemostasis. Perforation was defined as a full-thickness defect in the colonic wall with visible peritoneal fat during colonoscopy or existence of extra-gastrointestinal air on X-ray or abdominal CT after the procedure. These radiologic examinations were done only when perforation was suspected. The main endpoints of the present study are rates of post procedure bleeding and perforation. In addition, predictive factors for complication were evaluated. It was not regulated whether endoscopic clips are applied to the mucosal defect after endoscopic resection. Whether the patient should be hospitalized was determined by the endoscopist and was not regulated by the protocol. All the enrolled cases were followed up at 6 and 12 months by colonoscopy after the resection.

As for gross appearance, we divided the lesions into 5 types modified from the Japanese Rule for the Cancer of Colon and Rectum and the Paris Classification [12–14]: (1) pedunculated type (Ip), (2) sessile type (Is), (3) laterally spreading tumor granular type (LST-G), (4) laterally spreading tumor non-granular type (LST-NG), and (5) others.

For the final pathological diagnosis, we basically used the Vienna Classification with some modification; category 1: negative for dysplasia, category 2: indefinite for dysplasia, category 3: low grade dysplasia, category 4: high grade dysplasia, category 5: submucosal carcinoma [15, 16].

The statistical software package IBM SPSS Statistics Version 20 (SPSS Inc., Chicago, IL) was used to analyze the data. A multivariate analysis with binomial logistic regression was performed to clarify the relative risk for post procedure bleeding and perforation. All tests were two-tailed and P value less than .05 ($P < 0.05$) was defined as statistically significant. All data were collected and analyzed in a data center which was independent from any participating institute of the study.

Results

A total of 1,845 colorectal lesions $\geqq 20$ mm were enrolled for the cohort study; 1,029 lesions were treated with CER and the rest were treated with ESD. No patients had two or more lesions $\geqq 20$ mm. Among the 1,029 patients treated with CER, there were 637 men and 392 women (Table 1). The mean age was 65.2 ± 11.7 (20–89) years old. The location of the lesion was the rectum in 239 patients, sigmoid colon in 300, descending colon in 38, transverse colon in 161, ascending colon in 231, and cecum in 137. For the analysis, the colorectum was divided into the proximal and distal at the splenic flexure. The gross appearance of the lesion was Ip in 239, Is in 231, LST-G in 352, and LST-NG in 164. Polypectomy was performed in 163 and EMR in 866 lesions. The resection was en bloc in 586 lesions and piecemeal in 443. The final pathological diagnosis was Vienna classification category 1 or 2 in 24, category 3 in 502, and category 4 or 5 in 503 lesions.

Post procedure bleeding occurred in 18 cases (1.6 %). All of them received repeat colonoscopy, and bleeding was stopped with endoclips or hemostatic forceps. One case required blood transfusion. No surgery was necessary to treat the bleeding. We analyzed the following factors; age, gender, tumor size, location, gross appearance, treatment method, and pathological diagnosis, and conducted a multivariate analysis with binomial logistic regression (Table 2). Age-specific bleeding rate was highest among the forties and tended to decrease with age (Fig. 1). Statistical analysis among the age groups revealed that a significant difference of bleeding rate existed between the patients under 60 years old and those ≥60 years old. Perforation was encountered in 8 lesions (0.78 %), all of which had been resected with EMR technique. All of these perforations were diagnosed at the time of colonoscopy and there was no case with delayed perforation. The difference of perforation rate was not significant between EMR and polypectomy ($P = 0.46$). Only one case required surgery. The other cases were conservatively treated after the closure of the perforated site with endoclips. Vienna

Table 1 Clinicopathological characteristics of colorectal neoplasia

Gender	
Male	637
Female	392
Age(mean ± SD), years	65.2 ± 11.7
Tumor size (mean ± SD), mm	26.4 ± 8.6
Tumor location	
Rectum	162
Sigmoid colon	300
Descending colon	38
Transverse colon	161
Ascending colon	231
Cecum	137
Gross appearance	
Ip	239
Is	231
LST-G	352
LST-NG	164
Others	43
Treatment method	
EMR	866
Polypectomy	163
Pathology	
Category 1 or 2	24
Category 3	502
Category 4 or 5	503

Ip pedunculated type, *Is* sessile type, *LST-G* laterally spreading tumor granular type, *LST-NG* laterally spreading tumor non-granular type, *EMR* endoscopic mucosal resection

classification category 4–5 and en bloc resection were significant risk factors for perforation (Table 3). No procedure-related mortality was reported. The overall complication rate was 2.3 %.

Discussion

EMR and polypectomy are well-tolerated and cost-effective procedures in the management of large colorectal lesions. Our multicenter study also shows that CER is a safe and effective therapy for large colorectal lesions. Until recently, surgery has been a standard treatment for large early neoplasms. However, these lesions are frequently detected in elderly patients who are often associated with comorbidities and higher surgical risk. Endoscopic treatment of large sessile polyps is less invasive, avoids a major operation, and is also associated with fewer complications.

Clinically, post procedure bleeding and perforation remain the most common complications. According to the literature, the rate of post procedure bleeding after CER is reported to be between 0.4 and 7.0 % although the size of the subject lesions was varied [17–19]. In the present study, the post procedure bleeding rate for colorectal lesions sized $\geqq 20$ mm was 1.6 %. The multivariate analysis of the data revealed that the age under 60 years old is a risk factor for post procedure bleeding (OR = 6.53, 95 % CI 2.38–17.92). Kim et al. [20] reported that the average age of patients was lower in bleeding patients after colorectal endoscopic resection, but the difference was not statistically significant.

Table 2 Multivariable analysis of lesion characteristics, odds ratio, and 95 % confidence interval concerning post procedure bleeding

|		Bleeding	No bleeding	Odds ratio	95 % Confidence interval
Gender	Male = 0	12	625	0.74	0.27–2.05
	Female = 1	6	386		
Age	$\geqq 60 = 0$	6	730	6.53	2.38–17.92
	<60 = 1	12	281		
Tumor size	$\geqq 30$ mm = 0	6	294	0.90	0.31–2.66
	20–29 mm = 1	12	717		
Tumor location	Proximal = 0	12	517	0.46	0.16–1.32
	Distal = 1	6	494		
Gross appearance	LST-NG = 0	5	159	1.28	0.27–6.01
	Non LST-NG = 1	13	852		
Treatment method	EMR = 0	17	849	0.27	0.03–2.25
	Polypectomy = 1	1	162		
Resection type	en bloc = 0	10	576	0.89	0.32–2.52
	Piecemeal = 1	8	435		
Insufflation	CO2 = 0	9	409	0.81	0.30–2.18
	Room air = 1	9	602		
Pathology	Category 1–3 = 0	7	519	1.83	0.67–4.97
	Category 4–5 = 1	11	492		
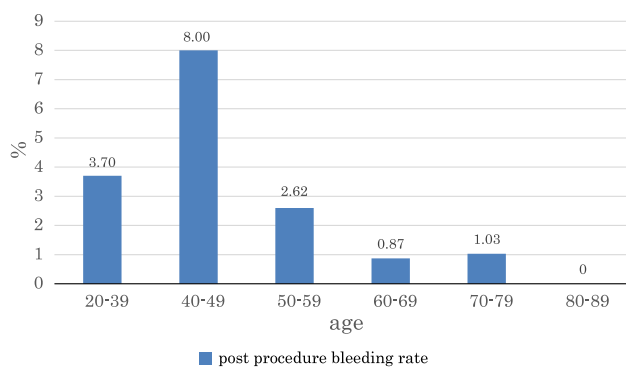
Fig. 1 Age-specific post procedure bleeding rate

To our best knowledge, this study is the first to show statistically higher incidence of bleeding in younger patients. No statistically significant difference of bleeding rate was found regarding gender, tumor size (between 20–29 mm and ≥30 mm), treatment method, gross appearance, kind of insufflation (CO_2 or room air), and pathology. Lim et al. [21] reported that complications were encountered more frequently when the lesion size was larger. In our study, we included only lesions ≥20 mm. There was no difference of bleeding rate between the lesions 30 mm or larger in diameter and those less than 30 mm. Bleeding rate is probably different between lesions <20 mm and those ≥20 mm, but may not increase any more even if the size becomes 30 mm or larger. Metz et al. reported that proximal location of the lesion is a highly significant risk for delayed bleeding following colonic EMR of large colonic lesions [20]. In our study, the bleeding rate in the proximal and distal colon (including the rectum) was not significantly

different. Fettata et al. reported that bleeding incidence was related to malignancy ($P = 0.01$) [22]. In the present study, 11 of 18 bleeding cases were encountered in lesions of Vienna classification category 4–5, but the rate was not significantly high (category 1–3 = 0, category 4–5 = 1, OR = 1.83, 95 % CI 0.67–4.97).

Araghizadef et al. [23] reported that the perforation rate of standard diagnostic colonoscopy was 0.09 %. Perforation related to endoscopic resection has been reported to be between 0.7 and 4 % [24–26] and higher than in diagnostic colonoscopy. The perforation rate was 0.78 % in the present study. Though we enrolled only lesions sized 20 mm or larger, the perforation rate was as low as the previous reports including smaller lesions. In this study, perforation was encountered in 8 lesions, all of which had been resected with EMR technique. Risk factors for perforation in multivariate analysis were en bloc resection (en bloc = 0, piecemeal = 1, OR = 0.08, 95 % CI 0.01–0.78) and category 4–5 (category 1–3 = 0, category 4–5 = 1, OR = 9.11, 95 % CI 1.03–80.79). According to our results, it is not recommended to adhere to en bloc resection in colorectal lesions ≥20 mm, as it may lead to perforation. No statistically significant differences of perforation rate were found regarding gender, size, tumor location, gross appearance, and kind of insufflation (CO_2 or room air).

Preference has been suggested in some studies for en bloc resection compared with piecemeal resection because it provides more accurate histological assessment and reduces the risk of local recurrence [27]. Hotta et al. reported that the en bloc resection rates were 91.5 % for colorectal neoplasms sized less than 20 mm and 43.0 % for

Table 3 Multivariable analysis of lesion characteristics, odds ratio, and 95 % confidence interval concerning perforation

		Perforation	No perforation	Odds ratio	95 % Confidence interval
Gender	Male = 0	5	632	0.89	0.20–3.96
	Female = 1	3	389		
Age	≧60 = 0	6	730	1.06	0.20–5.58
	<60 = 1	2	291		
Tumor size	≧30 mm = 0	3	297	0.53	0.11–2.47
	20–29 mm = 1	5	724		
Tumor location	Proximal = 0	6	523	0.27	0.05–1.48
	Distal = 1	2	498		
Gross appearance	LST-NG = 0	3	161	0.22	0.03–1.37
	Non LST-NG = 1	5	860		
Resection type	en bloc = 0	7	579	0.08	0.01–0.78
	Piecemeal = 1	1	442		
Insufflation	CO2 = 0	6	412	0.27	0.05–1.59
	Room air = 1	2	609		
Pathology	Category 1–3 = 0	1	525	9.11	1.03–80.79
	Category 4–5 = 1	7	496		

those sized 20 mm or larger [28]. Colorectal ESD technique is spreading gradually, but it is still very demanding due to its technical difficulty, long procedure time, and high rate of perforation. Nakajima et al. [29] reported that the en bloc resection rate for ESD was significantly higher than for CER. On the other hand, according to Kunihiro et al. [27], there was no statistically significant difference in the recurrence rate between en bloc and piecemeal resection groups. Endoscopic piecemeal mucosal resection for colorectal neoplasms $\geqq 20$ mm is usually useful. However, the area that suggests submucosal invasion should not cut in piece because it would interfere with a correct pathological diagnosis and because it might result in a local recurrence. In such cases, magnifying colonoscopy is very useful as it enables us to distinguish between neoplasia and non-neoplasia or between adenoma and carcinoma and to predict the degree of invasion. It is especially important to see if the lesion presents with type V pit pattern as it would indicate the lesion may be invasive [30].

In conclusion, CER is a safe, efficient, and effective minimally invasive therapy for large colorectal lesions. However, care should be taken for post procedure bleeding in patients under 60 years of age and for perforation in lesions with higher categories (4, 5) or when en bloc resection is tried.

The limitation of this study is rather small number of complications. It could not be avoided due to two reasons. One is that the present study is the subanalysis of the prospective study which was designed for a different main endpoint, and the power calculation was performed for that goal. The other reason is that the complication rate is sufficiently low enough in our endoscopic treatment and it would require vast number of lesions to establish a statistically significant difference among certain subgroups. In spite of the limitation, we believe that the results of this study are valuable as it is a multicenter prospective study which dealt with the largest number of colorectal lesions $\geqq 20$ mm so far to our best knowledge. Another study with larger scale is warranted.

Facilities that participated the study The patients were enrolled at the 18 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group of JSCCR as follows, 1) Digestive Disease Center, Showa University Northern Yokohama Hospital, Kanagawa, Japan (Yoshiki Wada, Shin-ei Kudo, Hiroshi Kashida), 2) Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan (Shinji Tanaka), 3) Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan (Yutaka Saito), 4) Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan (Hiroyasu Iishi),

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