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Original article

An evaluation of resectability among endoscopic treatment methods for rectal neuroendocrine tumors <10 mm

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ABSTRACT

Background and Study Aims: With respect to rectal neuroendocrine tumor (NET) resection, it remains unclear which of the following methods is the most effective: conventional endoscopic mucosal resection (cEMR), EMR using a fitted cap (EMR-C), EMR with a ligation band device (EMR-L), or endoscopic submucosal dissection (ESD). Thus, in this study, we aim to retrospectively evaluate the most effective endoscopic resection for rectal NETs < 10 mm.

Patients and methods: In total, 61 consecutive patients with primary rectal NETs < 10 mm in diameter were included in this study; they were then divided into three groups: those with cEMR; those with modified EMR (mEMR) involving EMR-C and EMR-L; and those with ESD. The primary endpoint was to evaluate the difference in the complete en bloc resection rate. The secondary endpoint was to investigate differences in procedure time and complications.

Results: Among the three groups, a significant difference was found in procedure time (cEMR vs ESD, $P < .01$; mEMR vs ESD, $P < .01$), en bloc resection rate (cEMR vs mEMR, $P = .015$), tumor size (mEMR vs ESD, $P < .01$), percentage of tumor diameter ≥ 5 mm (mEMR vs ESD, $P < .01$), and complete en bloc resection rate (cEMR vs mEMR, $P = .014$). Meanwhile, no significant difference was noted in terms of complication rate among the three groups.

Conclusion: The mEMR was the most suitable resection method for rectal NETs < 10 mm with respect to the risks and benefits from procedure-related factors, such as complete en bloc resection rate, procedure time, and complication rate.

Introduction

In recent years, the number of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) has been increasing [1]. GEP-NENs, especially gastrointestinal neuroendocrine tumors (GI-NETs), have been reported to have different primary site morbidities depending on their regional occurrence. In western countries, most primary lesions originate in the midgut, especially in the small intestine, whereas in East Asia, most primary lesions originate in the hindgut, especially in the rectum [2,3]. In Japan, epidemiological studies have reported that several GI-NETs are derived from the hindgut, with majority found in the rectum [4,5]. Recently, in Japan, due to the improvement of the health examination system, a large number of GI-NETs are detected during screening endoscopic examinations. Several of these are found incidentally, and most are lesions with a tumor diameter of around 5–10 mm [4]. In GI-NETs, tumor size, histological differentiation, proliferative index, and lymphatic invasion have been reported as risks of metastasis [6,7]. Of these factors, only tumor size can be accurately evaluated before treatment. Therefore, various guidelines recommend the endoscopic treatment of primary rectal lesions, especially small lesions, according to the tumor size [8-10]. For example, according to the National Comprehensive Cancer Network guidelines, endoscopic treatment is indicated for lesions < 20 mm within the submucosa and with no lymph node metastasis [9]; in relevant Japanese guidelines, lesions < 10 mm in diameter within the submucosa and without lymph node metastasis are indicated for endoscopic resection [10]. Regarding endoscopic treatment meth-

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ods, endoscopic mucosal resection (EMR), that is "injection and cut" method, has long been used [11]. Recently, various additional methods have been reported as modified EMR methods, such as EMR using a fitted cap (EMR-C), EMR with a ligation band device (EMR-L), and a two-channel method using a two-channel scope [11-13]. Furthermore, studies have shown the effectiveness of endoscopic submucosal dissection (ESD), which has now become widely practiced, and the options for endoscopic treatment have increased [11,14]. Although the efficacy of each endoscopic method has been reported, information on comparative resection rates, procedure times, and safety remain scarce. No guidelines specifically recommend which procedure to use for which lesion [15-18]. Therefore, we compared clinicopathological variables among endoscopic treatment methods in primary NETs of the rectum < 10 mm to determine which method offered the safest and most reliable option.

Patients and methods

Patients

We retrospectively reviewed 61 consecutive patients with primary rectal NETs < 10 mm who had undergone endoscopic resection at our institution from May 2003 to November 2019. All patients have signed a written informed consent prior to undergoing the procedures. For pretreatment evaluation, each patient was examined using computed tomography (CT) from the chest to the abdomen and through colonoscopy before treatment. All patients were confirmed as not having lymph node and distant metastasis through CT. Patients who had undergone chemotherapy or radiation therapy to the rectum or those with inflammatory bowel disease before endoscopic resection were excluded. When patients had synchronous multiple rectal NETs, the largest lesions were included in this study. We then divided the rectum into three segments, that is, rectosigmoid (RS), upper rectum (Ra), and lower rectum (Rb), according to the Japanese Society for Cancer of the Colon and Rectum guidelines [19]. The clinical staging of lesions was in accordance with the TNM classification of malignant tumors criteria [20]. Patients were divided into three groups: conventional EMR (cEMR) group; modified EMR (mEMR) group, including EMR-C and EMR-L; and ESD group. In this present study, we defined complete en bloc resection as a resection maneuver that was en bloc resected endoscopically and was pathologically free of lateral and longitudinal tumor invasion. Our Institutional Review Board approved this study (IRB No. 2015–0485).

Endoscopic procedures

In this study, videoendoscope systems (EVIS LUCERA SPECTRUM, EVIS LUCERA ELITE; Olympus Corporation Co., Ltd., Tokyo, Japan and LASEREO; FUJIFILM Co., Ltd., Tokyo, Japan), endoscopes with a single channel (PCF-Q260JI, GIF-Q260J; Olympus Corporation Co., Ltd., Tokyo, Japan and EG-L580RD; FUJIFILM Co., Ltd., Tokyo, Japan), and electrosurgical energy generators (ICC-200, VIO-300D, VIO-3; AMCO Co., Ltd., Tokyo, Japan) were used in resecting the lesions. All maneuvers in this study were performed by endoscopists who had >5 years of experience in gastrointestinal endoscopic treatment. The following methods were used, as described.

Conventional EMR (cEMR)

After an injection of saline solution with a small amount of indigo carmine into the submucosal layer below the tumor to raise the lesion from the muscularis propria, resection with an oval conventional snare was performed using an electrosurgical energy generator.

EMR using a fitted cap (EMR-C)

First, a saline solution with a small amount of indigo carmine was injected into the submucosal layer beneath the tumor. Second, after a snare loop, using a crescent-shaped electrosurgical snare (Olympus Corporation Co., Ltd., Tokyo, Japan), was formed in the transparent attachment with the groove of the rim (MAJ-290: Olympus Corporation Co., Ltd., Tokyo, Japan) that was fitted to the tip of the endoscope, the lesion was aspirated into the attachment. Finally, the lesion was snared, moved out of the attachment, and resected using an electrosurgical energy generator (Fig. 1).

EMR with a ligation band device (EMR-L)

After lifting the tumor from the muscularis propria using the saline solution with a small amount of indigo carmine, the lesion was sucked into a band ligation device (Sumitomo Bakelite Co., Ltd., Tokyo, Japan) attached to the tip of the endoscope and ligated at its base using the released band. Subsequently, resection with a snare was performed under the band using an electrosurgical energy generator (Fig. 2).

Esd

First, only the saline solution was injected into the submucosal layer to ascertain the appropriate submucosal layer elevation. Second, the saline solution with a small amount of indigo carmine, adrenaline, and 1% lidocaine was mixed with similar amount of 0.4% sodium hyaluronate solution (MucoUp; SEIKAGAKU CORPORATION Co., Ltd., Tokyo, Japan) and was injected into the submucosal layer. After lifting the tumor using submucosal injection, mucosal incision around the tumor and submucosal dissection below the tumor were performed using a Flush electrosurgical knife (FUJIFILM Co., Ltd., Tokyo, Japan) (Fig. 3).

Histopathologic evaluation

Specimens obtained by endoscopic resections were fixed in formalin, sectioned into 2–3 mm thick slices, and embedded in paraffin. Each specimen was histologically assessed for tumor size, depth of invasion, status of lymphovascular invasion (lymphatic spaces and blood vessels), and tumor invasion into the lateral and vertical margins. The World Health Organization 2019 classification criteria for grading tumors were employed when conducting evaluations using the Ki-67 labeling index or calculating the mitotic count [21]. Pathological stages were assessed using the TNM classification of malignant tumors criteria [20].

Endpoints

The primary endpoint in this study was to evaluate the difference in the complete en bloc resection rate between cEMR, mEMR, and ESD groups. The secondary endpoint was to assess differences in other procedure-related factors, such as procedure time and complication rates, between the three groups.

Statistical analysis

For the statistical comparisons of the clinicopathological factors in the three groups, the chi-square test or Fisher exact test was used for categorical data, whereas the Kruskal-Wallis test was used for continuous data. For pairwise comparisons, the chi-square test or Fisher exact test was used for categorical data, while the Mann-

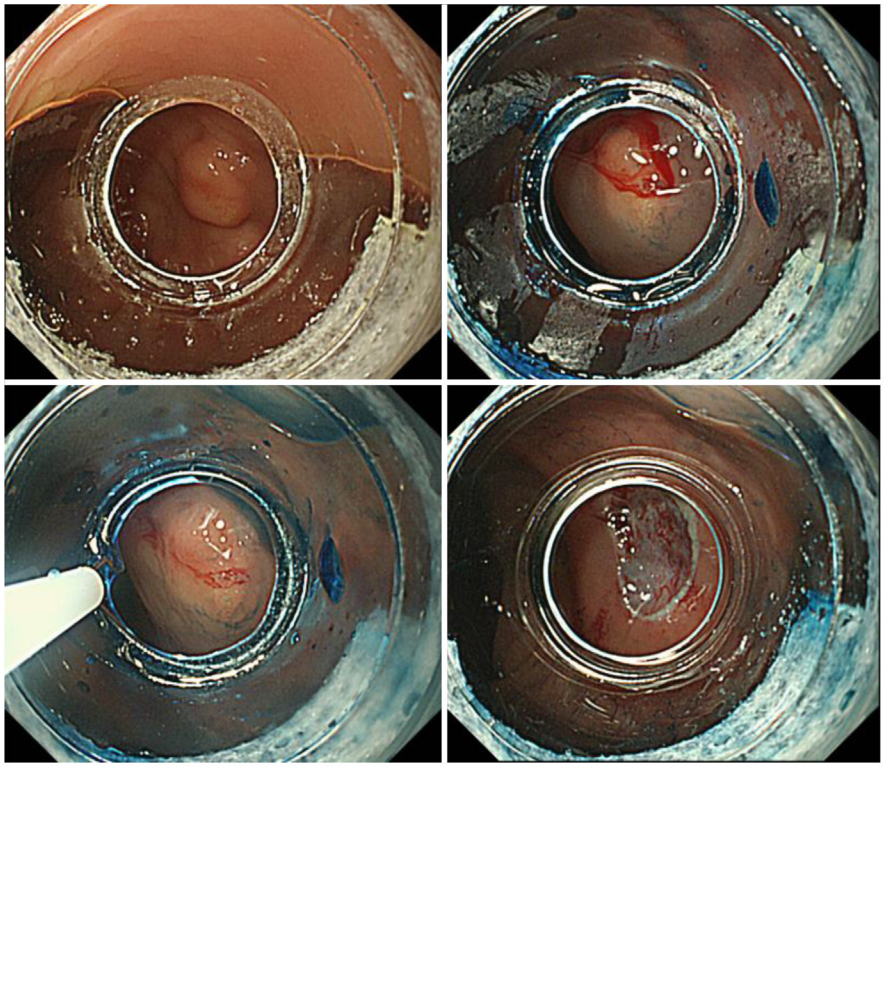

Fig. 1. Endoscopic mucosal resection with a fitted transparent cap (EMR-C) (a) An approximately 7-mm lesion in the lower rectum (Rb). (b) A saline solution with a small amount of indigo carmine was injected into the submucosal layer. (c) A crescent-shaped electrosurgical snare was positioned on the transparent attachment with the groove of the rim that was fitted to the tip of the endoscope. (d) After the lesion was aspirated into the attachment and resected: the post-EMR-C ulcer after en bloc resection.

Whitney *U* test with Bonferroni correction was used for continuous data. Continuous variables were expressed as medians with ranges. Significance was defined as probability values < 0.05 in comparisons among the 3 groups. In addition, significance was defined as probability values < 0.017 for the pairwise comparisons. Statistical analyses were performed with SPSS software (SPSS for Mac, version 26.0; SPSS, Chicago, IL).

Results

Clinicopathological characteristics between cEMR, mEMR, and ESD

In this study, 61 patients were examined, and their characteristics (male, 44; female, 17; median age, 57 [range, 32–87] years; tumor location, RS: 2, Ra: 5, Rb: 54; grading, G1: 60, G2: 1) are summarized in Table 1. Of the 61 rectal neuroendocrine tumors, 10 (16.4%), 27 (44.3%), and 24 lesions (39.3%) were treated by cEMR, mEMR, and ESD, respectively. Among these three groups, no significant differences were found concerning sex, age, tumor location, and procedure-related complications. The median procedure time was 3.9 (range, 3.0–42.0), 8.4 (range, 3.1–17.4), and 49.6 (range, 12.5–122.5) minutes in cEMR, mEMR, and ESD groups, respectively. The en bloc resection rates were 70.0%, 100.0%, and 100.0% in cEMR, mEMR, and ESD groups, respectively. Significant differences ($P < .01$) were observed in procedure time (cEMR vs mEMR, $P = .45$; cEMR vs ESD, $P < .01$; mEMR vs ESD, $P < .01$) and en bloc resection rate (cEMR vs mEMR, $P = .015$; cEMR vs ESD, $P = .02$; mEMR vs ESD, NA) (Table 2).

With respect to grading, depth of tumor invasion, lymphovascular invasion, and vertical and lateral margin involvement, no significant differences were found. The median tumor size was 3.8 (range, 2.0–8.0), 4.0 (range, 1.8–8.0), and 5.5 (range, 3.0–9.0) mm in cEMR, mEMR, and ESD groups, respectively. The percentage of tumor diameter $\geq$ 5 mm was 30.0%, 33.3%, and 75.0% in cEMR, mEMR, and ESD groups, respectively. Complete en bloc resection rates were 60.0%, 96.3%, and 91.7% in cEMR, mEMR, and ESD groups, respectively. Significant differences ($P < .01$) were noted in tumor size (cEMR vs mEMR, $P = .78$; cEMR vs ESD, $P = .055$; mEMR vs ESD, $P < .01$), percentage of tumor diameter $\geq$ 5 mm (cEMR vs mEMR, $P = .59$; cEMR vs ESD, $P = .02$; mEMR vs ESD, $P < .01$), and complete en bloc resection rate (cEMR vs mEMR, $P = .014$; cEMR vs ESD, $P = .048$; mEMR vs ESD, $P = .46$) (Table 2).

Resection rate by tumor size between mEMR and ESD

The en bloc resection rate was 100% for both mEMR and ESD for tumors < 5 mm in diameter and 100% for both mEMR and ESD for tumors > 5 mm in diameter. The complete en bloc resection rate was 100% for both mEMR and ESD for tumors < 5 mm in diameter and 88.9% and 88.9% for mEMR and ESD for tumors > 5 mm, respec-

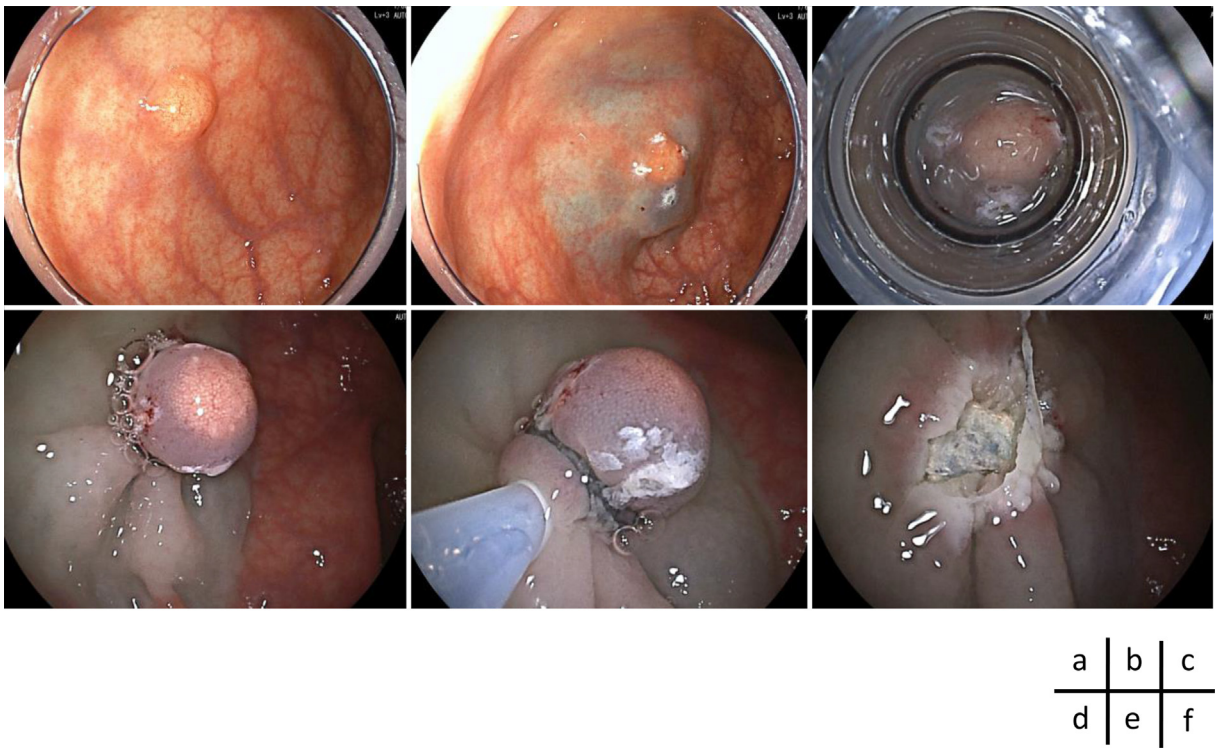

Fig. 2. Endoscopic mucosal resection with a ligation band device (EMR-L) (a) An approximately 5-mm lesion in the lower rectum (Rb). (b) Marking was performed on the entire lesion circumference, and a saline solution with a small amount of indigo carmine was injected into the submucosal layer. (c) The rectal neuroendocrine tumor was sucked into the cap of the ligation band device. (d) The tumor was then ligated using the elastic band. (e) Snare resection was performed under the band. (f) The post-EMR-L ulcer after en bloc resection.

tively, with no significant difference between the two groups (Table 3).

Recurrence after resection in cEMR, mEMR, and ESD groups

The median follow-up period after resection was 30.2 (range, 0.067–195.0), 34.8 (range, 14.2–113.2), 24.9 (range, 0.067–195.0), and 31.3 (range, 0.37–177.9) months for whole lesions, cEMR group, mEMR group, and ESD group, respectively. No recurrence was observed.

Discussion

With respect to rectal NETs, lesions < 10 mm in diameter have been reported as low risk of lymph node metastasis; according to various guidelines, endoscopic treatment is indicated for lesions < 10 mm [6,8-10]. In this study, we aimed to clarify the appropriate endoscopic treatment method for NETs of the rectum < 10 mm in diameter. As per our findings, it was determined that there was a significant difference in the en bloc resection rate and complete en bloc resection rate among the cEMR, mEMR, and ESD groups, and in multiple comparisons, there was a significant difference in the en bloc resection rate (P = .015, cEMR vs mEMR) and complete en bloc resection rate (P = .014, cEMR vs mEMR). Although no significant differences were found between the ESD and cEMR groups in terms of en bloc resection rate (P = .020, cEMR vs ESD) and in the complete en bloc resection rate (P = .048, cEMR vs ESD), the ESD group tended to have a higher resection rate compared to the cEMR group. Similar to this study, cEMR has been reported to have a low en bloc resection rate of 65.5%–82.1% [22-24], which may be due to the tumor origin [12,13]. Lee HJ et al. reported that 22 of the 47 cases resected using EMR had a positive vertical margin [25]. Rectal NET is a tumor derived from the deep mucosa that proliferates expansively and readily invades into the submucosa. Therefore, it has been considered challenging to snare with a sufficient vertical margin using cEMR or to sufficiently lift the tumor by injection into the submucosa. Cases of poor lift during injection into the submucosa have also been observed in the endoscopic treatment of colorectal tumors and reported as a sign of non-lifting [26,27]. When the non-lifting sign is positive, this suggests that, because the lesion may have infiltrated into the deep submucosa or may have strong fibrosis, en bloc resection with EMR is likely to be challenging. In this study, 3 of the 10 lesions in the cEMR group could not be resected en bloc, and 1 case had a positive vertical margin. In these cases, the non-lifting sign was observed as positive. Based on these results, EMR-C, EMR-L, and ESD have been used as the endoscopic treatment methods instead of cEMR, and their resection rates have exceeded 90% [11-13]. In this study, the mEMR group, which consisted of EMR-C and EMR-L cases, showed a high complete resection rate (96.3%) as well as the ESD group (91.7%), whereas the risk of developing complications was not different between the mEMR and ESD groups, and bleeding during endoscopic treatment was controlled in all cases. Therefore, both treatments can be considered useful for rectal NETs < 10 mm in diameter; however, the procedure time was significantly longer in the ESD group. Thus, this present study indicated that mEMR was preferable over ESD owing to the comparable resection and complication rates, although with a shorter procedure time. Although there are no definitive guidelines on the use of mEMR and ESD, there are some reports that suggested the selection of mEMR or ESD based on the tumor diameter [14]. In this study, the median tumor diameter was 4 and 5.5 mm in the mEMR and ESD groups, respectively. When 5 mm was taken as the cutoff, the ratio of lesions > 5 mm was significantly higher in the ESD group (P < .01). However, when comparing the en bloc resection and the complete en bloc resection

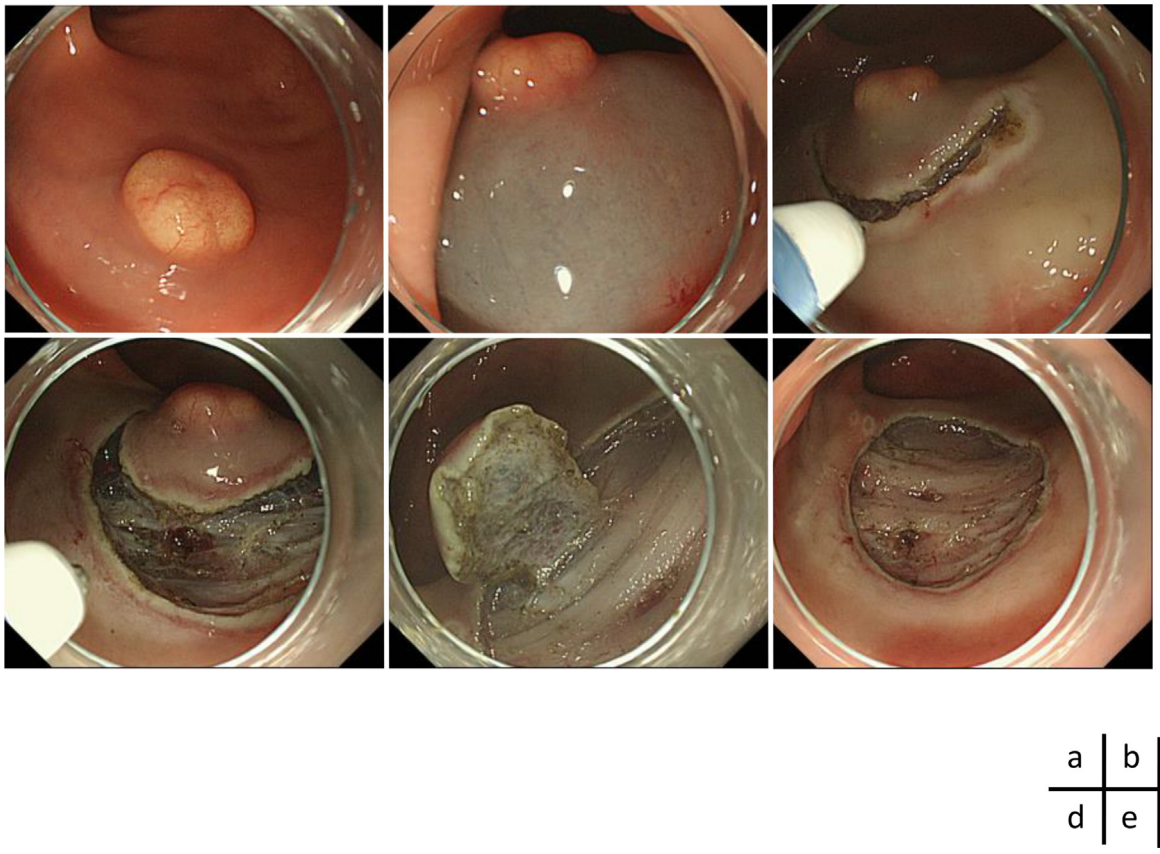

Fig. 3. Endoscopic submucosal dissection (ESD) (a) An approximately 7-mm lesion in the lower rectum (Rb). (b) A saline solution mixed with a small amount of indigo carmine, adrenaline, and 1% lidocaine was mixed with similar amount of 0.4% sodium hyaluronate solution and injected into the submucosal layer. (c) A mucosal incision was performed. (d, e) Submucosal dissection was performed with a Flush knife. (f) The post-ESD ulcer after en bloc resection.

Table 1
Clinicopathological characteristics of the patients.

Variable		Total (N = 61)
Sex	Male	44
	Female	17
Age (years)	Median(range)	57(32–87)
Tumor location	RS	2
	Ra	5
	Rb	54
WHO 2019 classification	G1	60
	G2	1
Endoscopic treatment method	cEMR	10
	EMR-C	14
	EMR-L	13
	ESD	24
Procedure time (min)	Median(range)	13(3–122.5)
En bloc resection n(%)		58(95.1)
Tumor size (mm)	median(range)	4(1.8–9)
Depth of tumor invasion	Submucosal layer	61
Vascular invasion	Positive	4
	Negative	57
Lymphatic invasion	Positive	2
	Negative	59
Vertical margin involvement	Positive	4
	Negative	57
Lateral margin involvement	Positive	1
	Negative	60
Complete en bloc resection n(%)		54(88.5)
Complication n(%)		4(6.6)
Postoperative bleeding n(%)		2(3.3)
Intraoperative perforation n(%)		2(3.3)

Abbreviations: cEMR: conventional endoscopic mucosal resection; EMR-C: EMR using a fitted cap; EMR-L: EMR with a ligation band device; ESD: endoscopic submucosal dissection; RS: rectosigmoid; Ra: upper rectum; Rb: lower rectum.

rates for lesions < 5 mm and those > 5 mm between the two groups, no significant differences were noted (Table 3). Given these results, a 5-mm tumor diameter could not be selected as a cutoff when choosing to use either mEMR or ESD. In this study, 9 of the 27 lesions > 5 mm were resected using mEMR, of which 8 had complete en bloc resection (Table 4). We used a cap with an 11-mm inner diameter for EMR-C and a band ligation device with an 8.5-mm inner diameter for EMR-L. Considering the inner diameter of the caps used in the mEMR group, it appears possible to safely resect a tumor > 5 mm using mEMR, although further research is required concerning the precise tumor diameter for which mEMR is indicated. In addition, we compared EMR-C cases and EMR-L cases in the mEMR group and found no significant differences in tumor diameter, resection time, complete en block resection rate, complications, or other parameters. The results of this study showed that in the mEMR group, EMR-C and EMR-L were considered to be equally positioned. This study showed that the median follow-up period after resection was 30.2 months; however, no recurrence was observed. Prognosis after the endoscopic treatment of primary rectal NETs has been reported to be good; the recurrence rate is low [28]. The overall survival concerning G1 and local lesions of the rectum, including those indicated for endoscopic treatment, is reported to exceed 30 years [1]. Endoscopic treatment appears useful in such cases.

This study had several limitations. First, this was a retrospective study in a single facility, involving a small number of lesions. However, we believe that the results of this study are meaningful because we consider this study to be a single-center, retrospective, exploratory study. In the future, we are considering validating the results of this study through a multicenter, prospective study. Sec-

Table 2
Clinicopathological characteristics among the resection methods.

Variable		cEMR (n = 10)	mEMR (n = 27)	ESD (n = 24)	*P*-value
Sex	Male	7	22	15	0.32**
	Female	3	5	9	
Age (years)	Median (range)	64.5 (49–76)	56 (34–87)	59 (32–81)	0.147*
Tumor location	RS	0	2	0	0.5***
	Ra	1	1	3	
	Rb	9	24	21	
Procedure time (min)	Median (range)	3.9 (3.0–42.0)	8.4 (3.1–17.4)	49.6 (12.5–122.5)	< 0.001*
En bloc resection n(%)		7(70.0)	27(100)	24(100)	0.003***
Complication n(%)		0(0)	3(11.1)	1(4.2)	0.51***
Postoperative bleeding n(%)		0(0)	2(7.4)	0(0)	0.646***
Intraoperative perforation n(%)		0(0)	1(3.7)	1(4.2)	1***
WHO 2019 classification	G1	10	27	23	1**
	G2	0	0	1	
Tumor size (mm)	Median (range)	3.8 (2–8)	4 (1.8–8)	5.5 (3–9)	0.014*
Tumor size ≧5 mm n(%)		3(30)	9(33.3)	18(75)	0.005***
Depth of tumor invasion	Submucosal layer	10	27	24	NA
Vascular invasion	Positive	0	2	2	1***
	Negative	10	25	22	
Lymphatic invasion	Positive	0	0	2	0.454***
	Negative	10	27	22	
Vertical margin involvement	Positive	1	1	2	0.653***
	Negative	9	26	22	
Lateral margin involvement	Positive	0	1	0	1***
	Negative	10	26	24	
Complete en bloc resection n(%)		6(60.0)	26(96.3)	22(91.7)	0.016***

*Kruskal-Wallis test, **chi-square test, ***Fisher exact test.
Abbreviations cEMR: conventional endoscopic mucosal resection mEMR: modified endoscopic mucosal resection ESD: endoscopic submucosal dissection RS: rectosigmoid Ra: upper rectum Rb: lower rectum NA: not available.

Table 3
Resection rate by tumor size among the resection methods.

Variable	mEMR(n = 27)	ESD(n = 24)	*P*-value*
En bloc resection rate %(n/N)			
<5 mm	100%(18/18)	100%(6/6)	NA
≥5 mm–<10 mm	100%(9/9)	100%(18/18)	NA
Complete en bloc resection rate (n/N)			
<5 mm	100%(18/18)	100%(6/6)	NA
≥5 mm–<10 mm	88.9%(8/9)	88.9%(16/18)	0.72

*Fisher exact test.
Abbreviations: mEMR: modified endoscopic mucosal resection; ESD: endoscopic submucosal dissection; NA: not available.

ond, tumor size was pathologically measured, and endoscopic ultrasonography (EUS) was not performed for all cases in this study. In the past, as reported by PK SB et al. [29], we found it challenging to perform EUS on all lesions, including the small ones. However, as described in the ENETS guidelines [8], the risk of lymph node metastasis is not zero even for lesions < 10 mm. Therefore, we now perform EUS on all patients to evaluate tumor size and locoregional lymph node metastasis to determine the treatment strategy. Third, there was a possibility of bias in the choice of resection method in this study. Although there have been reports of good results in the endoscopic treatment of rectal NETs, most of them were retrospective studies with small sample sizes; therefore, some of them recommended ESD for lesions > 5 mm [14], whereas others reported good resection results with EMR-L or EMR-C for lesions < 10 mm [12,13]. To date, there is no consensus on resection methods for lesions 5–10 mm in size, and there is no specific description of resection methods in the guidelines [8-10]. Therefore, in clinical practice, ESD was often chosen for lesions > 5 mm in Japan. In this study, the proportion of lesions > 5 mm was also higher in the ESD group. However, no significant difference was observed in the complete en bloc resection rate between mEMR and ESD for 5–10 mm lesions. These results also suggest that a prospective study is needed to determine the appropriate resection method for 5–10 mm lesions.

In conclusion, this study found that mEMR was the most suitable resection method for rectal NETs < 10 mm in diameter when considering the risks and benefits obtained by procedure-related parameters.

Table 4
Characteristics of lesions ≥ 5 mm in the mEMR group.

No.	Sex	Age	Location	Tumor size (mm)	RM	EBR	LVI	VM	LM	CEBR
1	F	53	Rb	5	EMR-C	YES	(−)	(−)	(−)	YES
2	F	51	Rb	5	EMR-L	YES	(−)	(−)	(−)	YES
3	M	38	RS	5	EMR-C	YES	(−)	(−)	(−)	YES
4	M	34	Rb	5	EMR-L	YES	(+)	(+)	(+)	NO
5	M	63	Rb	7	EMR-C	YES	(−)	(−)	(−)	YES
6	M	71	Rb	7	EMR-C	YES	(−)	(−)	(−)	YES
7	M	71	Rb	7	EMR-C	YES	(−)	(−)	(−)	YES
8	M	57	Rb	7	EMR-C	YES	(−)	(−)	(−)	YES
9	M	73	Rb	8	EMR-C	YES	(−)	(−)	(−)	YES

Abbreviations: RM: resection method; EBR: en bloc resection; LVI: lymphovascular invasion; VM: vertical margin involvement; LM: lateral margin involvement; EMR-C: endoscopic mucosal resection using a fitted cap; EMR-L: EMR with a ligation band device; CEBR: complete en bloc resection; Rb, lower rectum; RS, rectosigmoid.

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Declaration of Competing Interest

M.F. has received personal fees from Olympus, FUJIFILM, and HOYA Pentax, outside the submitted work. All other authors declare no conflict of interests for this article.

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