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Longly-attached cap can contribute to en bloc underwater endoscopic mucosal resection of 20–30 mm colorectal intramucosal lesions

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ABSTRACT

Background and study aims Underwater endoscopic mucosal resection (UEMR) is effective for colorectal intramucosal lesions. The aim of this study was to evaluate whether a longly-attached cap in UEMR improves the en bloc resection rate for 20–30 mm lesions.

Patients and methods We performed a retrospective study at a tertiary institute. Candidates for the study were systematically retrieved from an endoscopic and pathological database from October 2016 to December 2020. We assessed the procedural outcomes with UEMR for lesions ≥ 20 mm in size and the clinical factors contributing to en bloc resection.

Results A total of 52 colorectal lesions that underwent UEMR were included. The median procedure time was 271 (66–1264) seconds. The en bloc resection rate and R0 resection rate were 75 % and 73 %, respectively. Intraprocedural perforation occurred in one (1.9 %) case, but no bleeding occurred. Delayed bleeding occurred in one (1.9%) case, but no delayed perforation occurred. Regarding tumor size, macroscopic type, tumor location, and the presence or absence of a history of abdominal operation, there was no significant difference between the en bloc resection and piecemeal resection groups. The visibility of the whole lesion, a longly-attached cap, and sessile serrated lesions were more frequently observed in the en bloc resection group than in the piecemeal resection group ($P<0.001$, $P=0.01$, and $P=0.04$, respectively). Multivariate analysis showed that a longly-attached cap was the only independent factor associated with en bloc resection ($P=0.02$).

Conclusions A longly-attached cap might contribute to en bloc resection.

Introduction

Colorectal cancer is the fourth most common cancer in the world [1]. Endoscopic resection (ER) for colorectal intramucosal lesions is associated with a reduction in mortality from colorectal cancer [2]. ER methods comprise cold snare polypectomy (CSP), hot snare polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). EMR involves resection of the submucosa of a lesion using a snare and applying high-frequency current. EMR or ESD is recommended for lesions ≥ 20 mm in size in the guidelines of western and eastern countries [3–5].

ESD is recommended for laterally spreading tumors (LST) of the non-granular type (LST-NG) measuring ≥ 20 mm in size [5],

lesions suspected as submucosal invasive cancer [3], LST-granular type measuring ≥ 30 mm in size [5], and lesions with a diameter equal to or greater than half circumference [4].

In conventional EMR (CEMR), a normal saline solution or a sodium hyaluronate solution is locally injected into the submucosa of a superficial-type tumor through the injection needle [4]. Underwater endoscopic mucosal resection (UEMR) was reported in 2012 by Binmoeller et al. as a new method, during which the intestinal lumen is filled with water without injection into the submucosa [6]. UEMR is effective and safe compared with CEMR in resection of colorectal neoplasms measuring 10–20 mm [7–10]. UEMR is also performed for lesions measuring ≥ 20 mm as well as for lesions measuring 10–20 mm because of the simplicity and safety [11]. However, the en bloc resection rate with UEMR is not higher than that of ESD for lesions measuring 20–30 mm [12], and the local recurrence rate is high when piecemeal resection is performed in EMR or ESD [13–15]. Therefore, to take advantage of UEMR for lesions measuring ≥ 20 mm, new methods are required to improve the en bloc resection rate in UEMR. The aim of this study was to evaluate whether a longly-attached cap in UEMR improves the en bloc resection rate for 20–30 mm lesions.

Patients and methods

Patient selection

We performed a retrospective study at a single institute of a tertiary general hospital. We enrolled consecutive patients who underwent UEMR for colorectal lesions. We searched the pathological database using the words or phrases “UEMR” or “underwater EMR” and identified the patients who underwent UEMR from October 2016 to December 2020. Next, we confirmed the findings for all lesions using the endoscopic database, and we selected patients with 20–30 mm lesions. We assessed the procedural outcomes with UEMR for lesions measuring ≥ 20 mm in size and the clinical factors that contribute to en bloc resection.

The study protocol was approved by the institutional review board of our hospital, and the study was performed in accordance with the Declaration of Helsinki.

Diagnosis of colorectal lesions

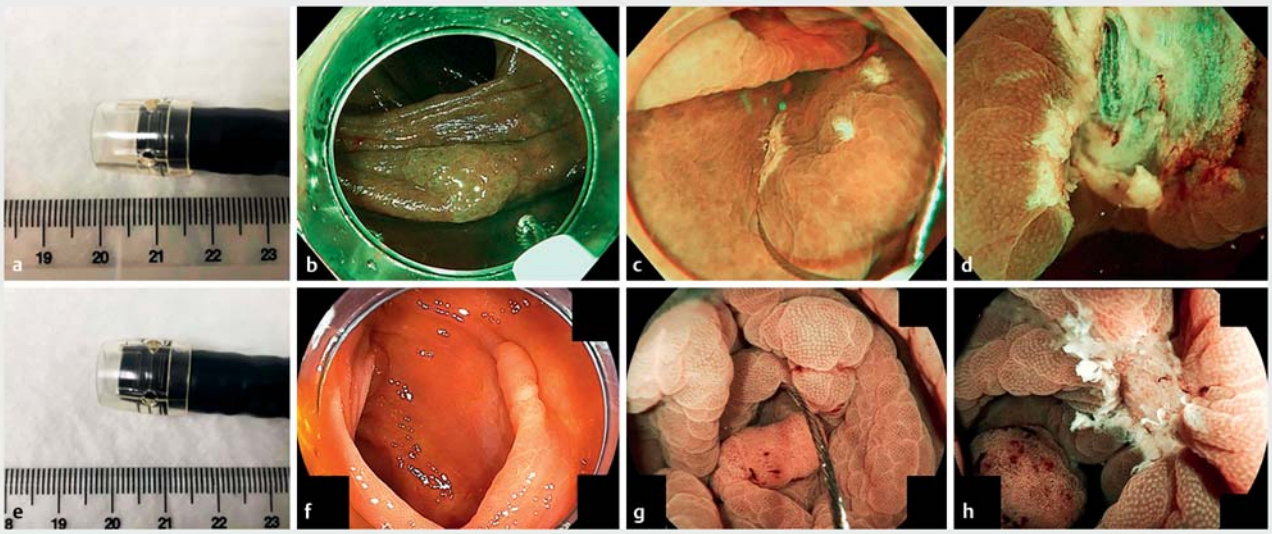
We evaluated the macroscopic type using the Paris classification of superficial neoplastic lesions [16]. We distinguished non-neoplastic lesions, adenomas, intramucosal carcinomas, submucosal invasive carcinomas, and sessile serrated lesions (SSL) based on the endoscopic images of the macroscopic findings and magnified findings with narrow-band imaging (NBI) using the Japan NBI Expert Team classification [17]. Adenoma and intramucosal carcinoma in the Japanese classification almost correspond to category 3 and 4 disease in the Vienna classification [18]. We also evaluated the lesions’ macroscopic features, such as expansive appearance, erosion/ulceration, convergent folds, stiffness, and elevated lesion in a depressed area to diagnose the invasion depth of the lesions, in accordance with previous reports [19, 20]. When the lesions were suspected to be submucosal invasive carcinoma, we also performed endoscopic ultrasonography, and then made a comprehensive diagnosis. We performed ER for neoplasms diagnosed as adenoma, SSL, and intramucosal carcinoma, as well as for large hyperplastic polyps, for which SSL cannot be ruled out. In ER, CSP, hot snare polypectomy, CEMR, UEMR, or ESD was chosen. In our institution, in accordance with guidelines from Western and Eastern countries [3, 4], we generally perform ESD for large lesions with a diameter equal to or greater than half the circumference of the lesion, or for lesions that are suspected to be submucosal invasive carcinoma; we perform EMR for other lesions. In EMR, UEMR or CEMR was chosen according to the endoscopists’ decisions. Lesions size was measured endoscopically, and it was confirmed during treatment by comparing it with the diameter of an opened snare (10–25 mm).

Procedures

Since 2016, we have performed UEMR as our standard treatment for lesions measuring 10–20 mm as well as for lesions measuring 20–30 mm in size, which are considered indications for EMR. The endoscopic procedures were performed using the following equipment: CF-HQ290ZI, PCF-H290ZI, or PCF-H290TI (Olympus Co., Tokyo, Japan) and EC-L600ZP7, EC-L600ZP7/L, or EC-L600XP7/L (Fujifilm Co., Tokyo, Japan). The following video endoscopy systems were used: EVIS LUCERA ELITE CV-290/CLV-290 (Olympus Co.) and LASEREO LL-7000/VP-7000 (Fujifilm Co.). The following caps were used: slit and hole types of adequate size for the endoscope (Top Co., Tokyo, Japan). In our institution, we have used the longly-attached cap for the last 2 years (▶ **Fig. 1b** [under air], ▶ **Fig. 1c** [underwater] and ▶ **Fig. 1d** [ulcer after resection]) because if the attached cap is short (▶ **Fig. 1f** [under air], ▶ **Fig. 1g** [underwater) and ▶ **Fig. 1h** [ulcer after resection]), its tip cannot be seen sufficiently with the natural magnification effect of water when the intestinal lumen is filled with water. We defined the length ‘longly’ when the full circumference of the tip could be seen in the monitor (▶ **Fig. 1b**). The distance between the tip of the cap and the tip of the endoscope was 7 mm with a longly-attached cap (▶ **Fig. 1a**). In contrast, we defined the length ‘not-longly’ when the full circumference of the tip could not be seen in the monitor (▶ **Fig. 1f**). The distance between the tip of the cap and the tip of the endoscope was 3 mm with an attached cap that was not long (▶ **Fig. 1e**). We used the same caps in the groups with the longly-attached cap and not longly-attached cap.

All procedures in this study were performed by a combination of trainer and trainee endoscopists. The trainers decided whether to perform the resection for all procedures even though the trainees were endoscopists. If the trainee found it difficult to perform en bloc resection, the trainer completed the procedure. Regarding endoscopist experience, experts were endoscopists with more than 10 years’ experience performing endoscopy. Non-experts were endoscopists with less than 10 years’ experience. As sedation, midazolam was used for almost all patients. Pentazocine hydrochloride was added if a patient had significant abdominal pain on endoscope insertion.

With SSLs, the demarcation line is often difficult to recognize underwater; therefore, we marked such lesions. After com-



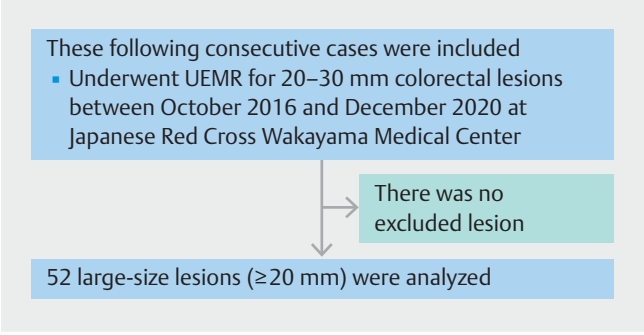
▶ **Fig. 1** **a** The length of the endoscope cap is sufficient. The distance between the tip of the cap and the tip of the endoscope is 7 mm in this image. **b** The length of the endoscopic cap is sufficient when the entire circumference of the tip of the cap can be seen in the monitor. **c** The cap can be recognized even when the intestinal lumen is filled with water. **d** The ulcer after resection. **e** The length of the endoscope cap is insufficient. The distance between the tip of the cap and the tip of the endoscope is 3 mm in this image. **f** The length of the endoscopic cap is insufficient when the entire circumference of the tip of the cap cannot be seen in the monitor. **g** The cap cannot be recognized when the intestinal lumen is filled with water. **h** The ulcer after resection.

plete deflation of air in the intestinal lumen, water was infused through the scope using a water jet function until the lumen was filled. The lesion was then grasped with a snare without submucosal injection [7]. While the whole lesion was recognized, the lesion was grasped fully. Generally, when we grasped the lesion, we obtained photographs of its margins or the markings, for SSLs. If the whole lesion could not be captured in a single photograph, images were taken of four locations – oral, anal, and left and right sides – to confirm that the whole lesion could be recognized. The visibility of the whole lesion was defined as the margin of the whole lesion recognizable in one or multiple photographs. After only a few seconds of pre-coagulation, the captured mucosa was transected. We resected the lesions using either a 10-, 15-, or 25-mm electrosurgical snare (Captivator II; Boston Scientific Co., Natick, Massachusetts, United States, or Snare Master Plus or Snare Master; Olympus, Tokyo, Japan). We used the following electrosurgical unit: VIO300 D (ERBE, Tübingen, Germany) which was set at Endocut Q mode (effect 2) and forced coagulation mode (effect 2, 40 W) or VIO3 (ERBE), which was set at Endocut Q mode (effect 3) and forced coagulation mode (effect 4.5). Procedure time was defined as the time from water infusion until confirmation of no residual lesion around the mucosal defect.

For each case, we attempted en bloc resection; however, if the attempt failed, we resected the lesion piecemeal. After we completed the resection, we carefully observed the mucosal defect to detect residual lesions in all cases. En bloc resection was defined as achieving complete lesion resection during a single procedure. Generally, the wound was closed completely using EZ clips (Olympus Co.) or Sureclips (Micro-Tech Co,. Nanjing, China). Patients were discharged the day after the procedure if they had no complications.

Intraprocedural bleeding was defined as spurting blood or persistent oozing that did not stop spontaneously within 60 seconds or following water irrigation, requiring endoscopic hemostasis with endoclips or coagulation. Intraprocedural perforation was defined as a defect in the muscle layer, with visualization of fatty tissue or other organs through the defect, which was confirmed during the ER procedure. Delayed bleeding was defined as bleeding requiring presentation to the emergency department, hospitalization, or medical intervention. Delayed perforation was defined as perforation occurring after the ER procedure, accompanied by free air or liquid detected by computed tomography or radiography, in the absence of any symptom or identification of perforation immediately after the ER procedure.

Resected specimens were embedded in paraffin and stained with hematoxylin and eosin (H&E). The specimens were assessed according to the Japanese Classification of Colorectal Carcinoma [21] by dedicated pathologists from our hospital. When the final pathological diagnosis of colorectal lesions was cancer, the pathologists also assessed lymphovascular infiltration on the basis of H&E staining and immunochemical staining as required. R0 resection was defined as en bloc resection, negative horizontal margin, negative vertical margin, and negative lymphovascular involvement.



▶ **Fig. 2** Patient enrollment.

Statistical analysis

Incidence (%) was used to describe categorical variables. Quantitative data were expressed as medians (ranges). For numerical variables, comparisons between groups were performed using the Mann–Whitney U-test, and for categorical variables, comparisons between groups were performed using Fisher's exact test. Factors independently associated with en bloc resection were assessed by multivariate logistic regression analysis. $P<0.05$ was considered to indicate statistical significance. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 3.3.3; The R Foundation for Statistical Computing, Vienna, Austria) [22] and SPSS software (version 22; IBM Corp., Armonk, New York, United States).

Results

Clinical characteristics of patients and lesions

Patient enrollment is shown in ▶ **Fig. 2**. A total of 483 colorectal lesions were treated with UEMR from October 2016 to December 2020 at our hospital; 52 colorectal lesions that underwent UEMR were included in this study. Clinical characteristics of patients are listed in ▶ **Table 1**. The median (range) lesion diameter was 20 mm (20–30). More than half the lesions were located in the ascending colon, and the macroscopic type of almost all lesions was 0–IIa.

▶ **Table 1** Clinical characteristics of patients and lesions.

		52 lesions
Age, median (range), y		71 (38–83)
Sex	Male:female	30 (58):22 (42)
Lesion size, median(range), mm		20 (20–30)
Location	A:T: D:S:R	28 (54):12 (23):3 (6):5(9):4(8)
Macroscopic type	Is:IIa	12 (23):40 (77)
Use of antispasmodic agents	Yes:no	52 (100):0
Cap length	Long:not long	39 (75):13 (25)

Values are number (%), except where otherwise indicated.
A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum.

▶ **Table 2** Outcomes with UEMR and results of pathological examinations.

		52 lesions
Procedure time (second)	Median (range)	271 (66–1264)
En bloc resection		39 (75)
Number of resections in piecemeal	Median (range)	2 (2–5)
Intraprocedure adverse events	Bleeding	0
	Perforation	1 (1.9)
Delayed adverse events	Bleeding	1 (1.9)
	Perforation	0
Pathological type	Tubular adenoma: Tis: SSL	33 (63): 3 (6): 16 (31)
R0 resection		38 (73)

Values are shown as number (%), except where otherwise indicated.
UEMR, underwater endoscopic mucosal resection; SSL, sessile serrated lesion.

Procedural outcomes with UEMR

▶ **Table 2** shows procedural outcomes with UEMR. Median procedure time was 271 (66–1264) seconds. The en bloc resection and R0 resection rates were 75 % and 73 %, respectively. In piecemeal resection cases, the median number of resections was two (2–5). All lesions were intramucosal tumors and all were negative for lymphovascular involvement.

Intraprocedural and delayed bleeding occurred in none and one case (1.9 %), respectively. Intraprocedural and delayed perforation occurred in one (1.9 %) and no cases, respectively. Delayed bleeding occurred on the 13th day after the procedure for a 20-mm lesion in the descending colon in a 73-year-old man. Emergent endoscopic hemostasis was performed, and he recovered. Intraprocedural perforation of a 20-mm lesion in the sigmoid colon occurred in a 75-year-old man. The muscularis defect was completely closed using clips, and the patient was discharged without requiring surgery. There were no patients with specific complications related to UEMR, such as electrolyte abnormalities.

Clinical factors associated with en bloc resection

▶ **Table 3** shows results of the univariate analysis of the factors associated with en bloc resection. Regarding lesion location, tumor size, macroscopic type, presence or absence of a history of abdominal operation, presence or absence of marking the lesion with soft coagulation, size of the snare, and endoscopist experience, there were no significant differences between the en bloc resection and piecemeal resection groups. In contrast, the visibility of the whole lesion when snaring the lesion, longly-attached cap, and pathological type of SSL were more frequent

▶ **Table 3** Clinical factors associated with en bloc resection (univariate analysis).

		En bloc resection N = 39	Piecemeal resection N = 13	*P* value
Location	Ascending colon	23	5	0.12
	Transverse colon	7	5	
	Descending colon	1	2	
	Sigmoid colon	5	0	
	Rectum	3	1	
Size (mm)		20 (20–30)	20 (20–30)	0.78
Macroscopic type	0-I	10	2	0.71
	0-IIa	29	11	
Abdominal operation's history	Yes	14	3	0.51
	No	25	10	
Marking	Yes	12	1	0.14
	No	27	12	
Size of snare	10 mm	1	0	1
	15 mm	17	6	
	20 mm	20	7	
	25 mm	1	0	
Endoscopist experience	Expert	22	6	0.54
	Non-expert	17	7	
Visibility of the whole lesion	Yes	38	3	<0.001
	No	1	10	
Cap length	Long	33	6	0.01
	Not long	6	7	
Pathological type	SSL	15	1	0.04
	Adenomatous lesion	24	12	
Procedure time		240 (66–1264)	511 (220–1067)	0.001

Values are presented as numbers.
SSL, sessile serrated lesion.

in the en bloc resection group ($P = 0.04$, $P < 0.001$, and $P = 0.01$, respectively). Of the three items, visibility of the whole lesion and longly-attached cap were correlated (▶ **Table 4**), and logistic regression analysis was performed using longly-attached cap, SSL, and endoscopist experience. (Endoscopist experience was included as a variable because it could affect the outcome). Multivariate analysis showed that use of a longly-attached cap was an independent factor associated with en bloc resection ($P = 0.02$) (▶ **Table 5**).

Discussion

To the best of our knowledge, this is the first study to investigate clinical factors that contribute to en bloc resection with UEMR for lesions measuring ≥ 20 mm in real-world practice. In this study, it was shown that a longly-attached cap may contribute to en bloc resection with UEMR for colorectal intramucosal lesions measuring 20–30 mm.

In ER for colorectal intramucosal lesions, piecemeal resection is considered a risk factor for residual recurrence [13–15], and en bloc resection is generally required. Guidelines regarding intramucosal lesions recommend choosing a resection method according to lesion size, such as the following: CSP for adenomas < 10 mm [3, 23], EMR for lesions 10–20 mm [4], and EMR or ESD for lesions ≥ 20 mm or that measure more than half

▶ **Table 4** Correlation coefficient analysis.

		Visibility of whole lesion	Longly-attached cap	Pathological type of SSL
Visibility of whole lesion	Pearson's correlation coefficient	1	.462	.141
	Significance probability (two-sided)		.001	.318
	Number	52	52	52
Longly-attached cap	Pearson's correlation coefficient	.462	1	.192
	Significance probability (two-sided)	.001		.172
	Number	52	52	52
Pathological type of SSL	Pearson's correlation coefficient	.141	.192	1
	Significance probability (two-sided)	.318	.172	
	Number	52	52	52

SSL, sessile serrated lesion.

▶ **Table 5** Clinical factors associated with en bloc resection (multivariate analysis).

		Multivariate analysis	
		Odds ratio (95% CI)	*P* value
Longly-attached cap	Yes/no (reference)	6.01 (1.30–27.90)	0.02
SSL	Yes/no (reference)	6.49 (0.70–60.30)	0.10
Endoscopists' experience	Expert/non-expert (reference)	1.37 (0.30–6.18)	0.68

SSL, sessile serrated lesion; CI, confidence interval.

the lesion's circumference [3–5]. The reason for the recommendation to perform EMR or ESD for lesions ≥ 20 mm is that with larger lesions, rates of piecemeal resection or submucosal invasion increase [4–15]. Therefore, UEMR can be an effective alternative for intramucosal tumors measuring 20–30 mm if the en bloc resection and complication rates with UEMR are comparable to rates with ESD or CEMR for these lesions. Therapeutic results with UEMR, CEMR, and ESD were evaluated by comparing our results with those in a previous study of ESD [12]. Procedure time, en bloc resection rate, R0 resection rate, and adverse event (AE) rates with UEMR for intramucosal tumors measuring 20–30 mm in our study were 4.5 minutes, 75%, 73%, and 3.8%, respectively; those for ESD in a previous study were 64.8 minutes, 99%, 86%, and 5.9%, respectively [12]. UEMR appears to be associated with shorter procedure time and a lower incidence of AEs, despite the lower en bloc resection rate with UEMR compared with ESD. The en bloc resection rate and AE rate with CEMR for lesions measuring 20–30 mm in a meta-analysis were 45% and 6.2%, respectively [24]. UEMR appears to be associated with a higher en bloc resection rate and lower AE rate compared with CEMR.

It is essential to squeeze the whole lesion with a snare for en bloc resection. To achieve this, it is important to visualize and recognize the whole lesion when squeezing the lesion, and we considered that a longly-attached cap could contribute to achieving this result. The reason is that the oral side of large lesions is sometimes located between or behind the folds and is difficult to recognize. With a longly-attached cap, the folds can be divided, which makes it easier to recognize both the anal and oral sides of the lesion, which permits en bloc resection. In fact, in this study, there was an association between visibility of the whole lesion and a longly-attached cap in the correlation analysis. In addition, clinically, when peristalsis is strong or the lesion straddles a fold, it is sometimes difficult to recognize the whole lesion using a shortly-attached cap. In contrast, with a longly-attached cap, we often achieve a better endoscopic view and can visualize the whole lesion in such situations. Therefore, the results of this study match the clinical impression. Furthermore, underwater, endoscopic observation is slightly magnified, and the cap appears to be shorter owing to refraction. Therefore, with a short attached cap, recognizing the whole lesion is often difficult, and structures such as folds obstruct visibility. In contrast, using a longly-attached cap may have disadvantages. First, the endoscopic view becomes small owing to the cap. Second, the possibility that the polyp detection rate may be lower than without a longly-attached cap cannot be denied. Therefore, we do not use a longly-attached cap for screening endoscopy. However, with a longly-attached cap, there are no difficulties when performing UEMR, including performing clipping after resection, in our experience. We use a

longly-attached cap in all UEMR cases. A longly-attached cap is useful for both large and small lesions, in our experience. We have not experienced disadvantages when using a longly-attached cap compared with using a shortly-attached cap. We attach the cap longly to the endoscope only when we plan to perform UEMR. Regarding the safety of a longly-attached cap, there was only one case of perforation in this study. The perforation occurred because the lesion could not be maneuvered into an ideal position for resection. Generally, the muscle layer is not suctioned during UEMR; therefore, the perforation rate with UEMR is not high [7].

In univariate analysis, the en bloc resection rate was high with SSLs. The reason for this finding is unclear, but there are several possible explanations. First, marking is often performed for SSLs because the margins of SSLs are sometimes vague compared with adenomatous lesions. Therefore, marking would help when squeezing the lesion. Second, SSLs often have no nodules and are flat. These macroscopic features may make it easier to squeeze the lesion. Although SSL had a similar odds ratio to the longly-attached cap, SSL was not a significant independent factor in multivariate analysis. This result could be owing to the small sample size, and prospective RCTs with large sample sizes are required to confirm this finding.

When a lesion measuring 20–30 mm is suspected to be high-grade dysplasia or intramucosal cancer and en bloc resection by CEMR is difficult, ESD is often considered. However, ESD requires greater expertise and is associated with more complications compared with EMR [25, 26]. ESD also has more disadvantages than EMR regarding hospitalization duration and cost [12]. Moreover, ESD is sometimes difficult owing to patient background or lesion location. In addition, two meta-analyses [24, 27] showed that the en bloc resection rate with UEMR was higher than that with CEMR for lesions measuring ≥ 20 mm. Moreover, there was no significant difference in AE rates between UEMR and CEMR [26]. Therefore, UEMR could be a strategy for resection of larger lesions if it can achieve a better en bloc resection rate. The results of the current study showed that a longly-attached cap can contribute to a better en bloc resection rate with UEMR.

The advantages of UEMR are the following. First, additional expertise is not required [12]. Second, UEMR is possible even in facilities where ESD is not performed commonly. Third, UEMR can be completed in a short time. Outcomes with UEMR for intramucosal lesions measuring 20–30 mm in this study were not much different from the previously reported outcomes with UEMR for lesions measuring 10–20 mm. However, UEMR is inferior to ESD regarding en bloc resection, and accurate pathological evaluation is difficult when piecemeal resection is performed. In addition, there is a risk of residual recurrence [28]. Therefore, if the en bloc resection rate of UEMR can be increased, ER for large colorectal intramucosal tumors will be possible even in general hospitals in which ESD is not performed often.

This study has several limitations. First, it was a retrospective study in a single facility. However, our findings will aid in the performance of future prospective studies. Second, the selection of the treatment method depended on each endoscopist's opinion. However, including endoscopists' experiences, clinical factors were not significant in the univariate analysis except for the visibility of the whole lesion, a longly-attached cap, and the pathological type of SSL. Third, the number of detected lesions was small. Fourth, strictly speaking, the evaluation of whether the whole lesion was visible may not have been accurate even though we tried our best to maintain a monitor image in which the whole lesion was visible. This is one of the reasons that we selected a longly-attached cap in the multivariable analysis because cap length is more objective than visibility of the whole lesion.

Conclusions

In conclusion, a longly-attached cap was associated with visualization of the whole lesion and was considered to provide a better effect for en bloc resection. However, a prospective RCT is required to verify our results.

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Competing interests

The authors declare that they have no conflict of interest.

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