

Resection depth and layer of underwater versus conventional endoscopic mucosal resection of intermediate-sized colorectal polyps: A pilot study



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ABSTRACT

Background and study aims Curability of colorectal tumors is associated with resection depth and layer in endoscopic resection. Underwater endoscopic mucosal resection (UEMR) has not undergone sufficient histopathological evaluation. We conducted a pilot study to compare the effectiveness, including resection depth and layer, of UEMR and conventional endoscopic mucosal resection (CEMR).

Patients and methods This study was a single-center, retrospective study. Patients with colorectal lesions were treated by UEMR or CEMR between January 2018 and March 2020. Eligible patients were selected from included patients in a 1:1 ratio using propensity score matching. We compared the resection depth and layer and treatment results between the UEMR and CEMR groups.

Results We evaluated 55 patients undergoing UEMR and 291 patients undergoing CEMR. Using propensity score matching, we analyzed 54 lesions in each group. The proportion of specimens containing submucosal tissue was 100% in both groups. The median thickness of the submucosal tissue was significantly greater in the CEMR group than in the UEMR group [1235 μ m (95% confidence interval [CI], 1020–1530 μ m) vs. 950 μ m (95% CI, 830–1090 μ m), respectively]. However, vertical margins were negative in all lesions in both groups.

Conclusions Our findings suggest that the median thickness of submucosal tissue in the UEMR group was about 1,000 μ m. Even though the resection depth achieved with UEMR was more superficial than that achieved with CEMR, UEMR may be a treatment option, especially for colorectal lesions \leq 20 mm in diameter without suspicious findings of submucosal deeply invasive cancer.

Introduction

Colorectal cancer (CRC) is among the most common malignancies and remains the second leading cause of cancer-related death globally [1]. Endoscopic resection (ER) of colorectal polyps has been shown to reduce CRC-related mortality [2, 3]

and therefore plays an integral role in CRC prevention. Thus, improvements in ER techniques are of paramount importance.

The focus of ER is now on en bloc resection rather than piecemeal resection [4]. Polyp size is an independent predictor of the ability to perform complete resection or en bloc resection [5]. Conventional endoscopic mucosal resection (CEMR) is a

standard method for removing sessile colorectal polyps larger than 10 mm [6–8]. A relatively new technique of water immersion endoscopic mucosal resection, referred to as underwater endoscopic mucosal resection (UEMR), described by Binmoeller et al. in 2012, was proposed as an alternative to CEMR [9]. UEMR is performed by suctioning out gas from the colonic lumen and instilling water immediately before polyp resection. Filling the colon lumen with water instead of gas decreases wall tension and has a buoyancy effect on the mucosa and submucosa, raising them above the muscularis layer without the need for submucosal (SM) injection. This changes the borders and shape of a lesion, potentially making it easier to resect completely with snaring. The efficacy of UEMR for clinically significant (≥ 10 mm) colorectal polyps was previously reported [10]. Additionally, a multicenter, randomized controlled trial reported that UEMR significantly increased the R0 resection rate for 10–20 mm sessile colorectal lesions without increasing adverse events or the procedure time [11].

SM invasive cancer is quite rare, being 0.1% in colorectal polyps <10 mm in size, but the rate of SM invasive cancer is as high as 4.2% in lesions measuring 10 to 20 mm in size [12]. In contrast to CEMR, with UEMR, the bowel lumen is filled with water, and the lesion is captured and resected with a snare without SM injection of normal saline. We therefore hypothesized that resection depth with UEMR is less than that with CEMR and that the submucosa may not be adequately resected with UEMR. However, to our knowledge, there has been no study that has assessed resection depth and layer of colorectal polyps with UEMR. Therefore, we conducted a pilot study using propensity score matching to evaluate the resection layer and depth of UEMR specimens and compare results of endoscopic removal of intermediate-sized (10–20 mm) sessile colorectal lesions (including adverse events) by UEMR versus CEMR.

Patients and methods

Study design and patients

This study was a single-center, retrospective study. Inclusion criteria were patients with colorectal lesions that were 10 to 20 mm in diameter and treated by UEMR or CEMR between January 2018 and March 2020 at Ishikawa Prefectural Central Hospital. In cases where multiple lesions were treated, the first lesion treated was included. The lesion size was initially estimated according to its endoscopic appearance or by comparison with the size of opened (~ 7 mm) or closed (~ 2 mm) biopsy forceps, and it was confirmed at the treatment session by comparison with an opened snare (13 mm). Exclusion criteria included pedunculated lesions and lesions in which the specimen was fixed in a bent or curled position, which made it difficult to measure the exact depth of resection of the specimen. We used propensity score matching to compare the clinical outcomes between the UEMR and CEMR groups, as described below.

We performed this retrospective study at our hospital in Japan. The hospital's institutional review board approved the collection of data, examination of past cases, and submission of the results in this study (approval no. 1626), and written informed consent was obtained from all patients.

Procedures

The nine endoscopists who had performed more than 200 EMRs prior to this study performed the ER. During the study period, four of nine endoscopists performed UEMRs and all endoscopists performed CEMRs. All detected polyps were evaluated by endoscopy with white light and magnifying narrow-band imaging (M-NBI). We used the electronic endoscopy system with NBI (Evis Lucera Spectrum System, Olympus Medical Systems Corp., Tokyo, Japan) and high-resolution optical magnifying colonoscopes with an auxiliary water jet (Evis CFH260AZI or PCF-Q260AZI; Olympus). To facilitate the identification and diagnosis of colonic lesions, M-NBI was used in addition to white light observation. Lesions were detected using the white light mode. The location, size, and macroscopic type of all detected lesions were documented according to the Paris classification [13]. The location of each polyp was determined on the basis of the anatomic features of each colonic segment. The final selection of UEMR or CEMR was dependent on each endoscopist's preference.

The UEMR procedure included the following (► **Fig. 1**): 1) complete deflation of the colorectal lumen; 2) total immersion of the lesion in normal saline using a mechanical water pump (OFP-2; Olympus); 3) snaring of the lesion and the surrounding mucosa; and (4) resection of the lesion using electrocautery. We used a hexagonal electrocautery snare (Captivator Small-Hex; Boston Scientific, Marlborough, Massachusetts, United States). The electrosurgical generator's (ESG-100; Olympus) cautery setting was PulseCut slow 60 W.

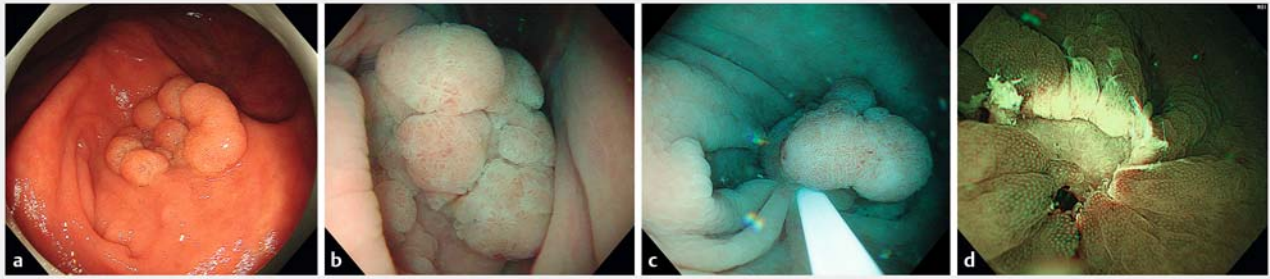
The CEMR procedure included the following: 1) needle injection of normal saline into the submucosa; 2) entrapment of the mucosal protrusion with a snare; and 3) resection applying the same electrocautery setting as was used for UEMR. We used a hexagonal electrocautery snare (Captivator SmallHex; Boston Scientific) or an oval electrocautery snare (Sensation Short Throw Snare; Boston Scientific).

In both groups, en bloc resection of all polyps was attempted whenever possible. After ER, the edge of the resection wound was carefully examined. If a remnant lesion were apparent or suspected, it was resected using the same method until complete removal was achieved. If intraprocedural bleeding occurred, it was treated by electrocoagulation with a snare tip (soft coagulation 80 W) or with hemostasis clips (EZ Clip; Olympus). Postoperative mucosal defects were routinely closed using clips.

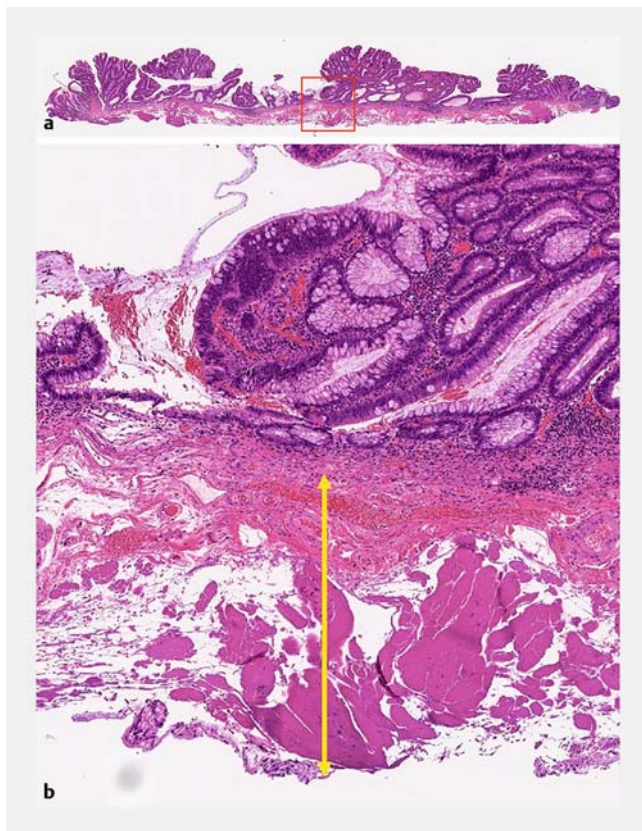
Follow-up was done in an outpatient clinic visit 4 to 7 days after the procedure to monitor bleeding, perforation, and any other adverse events.

Measured outcomes

Our main outcome measure was resection depth using specimens obtained by UEMR or CEMR. Histological evaluation of specimens was used to determine whether SM tissues were contained under the neoplastic mucosa or at the center of the resected specimens. Furthermore, when the specimens contained SM tissue, SM tissue thickness was measured as resection depth (► **Fig. 2**).



► **Fig. 1** Endoscopic procedure for underwater endoscopic mucosal resection (UEMR). **a** White light endoscopy showing a granular-type, laterally spreading tumor in the cecum with a diameter of approximately 20 mm. **b** White light endoscopy showing the underwater appearance of the same lesion as in **Fig. 1a**. **c** White light endoscopy showing underwater resection with a snare. **d** Narrow-band imaging showing the wound after UEMR, with no residual lesion.



► **Fig. 2** Histopathologic findings after underwater endoscopic mucosal resection (hematoxylin and eosin stain). **a** The resected specimen contained muscularis mucosa and submucosal tissue. The final histopathological diagnosis was intramucosal adenocarcinoma. **b** Histopathological findings of the red box in **Fig. 2a**. The thickness of submucosal tissue (double-headed arrow) is 701 μm .

Treatment outcomes, including en bloc resection, histologic and endoscopic complete resection, delayed postprocedural bleeding, and perforation were also evaluated. En bloc resection was defined as one-piece resection without any visible residual tissue on conventional white light imaging and M-NBI. R0

resection was defined as en bloc resection with a histologically confirmed negative resection margin.

Safety endpoints included delayed bleeding within 7 days after resection and delayed perforation. Delayed postprocedural bleeding was diagnosed upon the onset of hematochezia after polypectomy. Perforation was diagnosed when the extramural organ or fat outside the muscle layer was visualized by endoscopy or free air was observed on computed tomography. We compared these outcomes between the UEMR and the CEMR groups.

Histopathological evaluation

After resection, the specimens were retrieved, immersed in 10% formalin, and sent for histological assessment. The fixed specimens were sectioned serially at 2- to 3-mm intervals and then assessed by two experienced pathologists. Histopathological diagnosis of the lesion and involvement of the resection margin were evaluated according to the Japanese Classification of Colorectal Carcinoma [14]. Representative samples from the central part of the lesion were extracted from multiple ER specimens. Using a virtual pathology system (Aperio eSlide Manager; Leica Microsystems GmbH, Wetzlar, Germany), the resection depth and presence/absence of the submucosa were evaluated. Resection depth was determined using the SM tissue thickness from the muscularis mucosa to the vertical resection margin in the relatively thick part near the center, which was vertically measured as described in a previous report [15]. Under the guidance of a pathologist (H.M.), all specimens were reviewed by two of the authors (H.N. and S.T.) on a computer display using a virtual pathology system. Inter-observer variation was resolved by reevaluation utilizing a virtual pathology system and discussion to reach a consensus in the case of a discrepancy.

Statistical analysis

Continuous variables, presented as medians, were compared using the Mann-Whitney U-test, and categorical variables were compared using the chi-squared test and Fisher's exact test. We have presented categorical outcomes as frequencies and percentages with 95% confidence intervals (CIs), and continuous outcomes as medians and 95% CIs. The CIs for the

medians were conducted using a bootstrap method. To adjust for potential confounders, we used propensity scoring to match each UEMR lesion with one CEMR polyp. We used a multivariate logistic regression model to calculate propensity scores for undergoing UEMR and performed 1:1 greedy matching algorithm within a caliper width of 0.2 standard deviation of the propensity score. Lesion size, lesion location, and morphology, all of which possibly affect the selection of UEMR or CEMR, were used to generate the propensity scores [11]. $P < 0.05$ was considered statistically significant. Because the present study was exploratory, no correction for multiple comparisons was performed. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics [16].

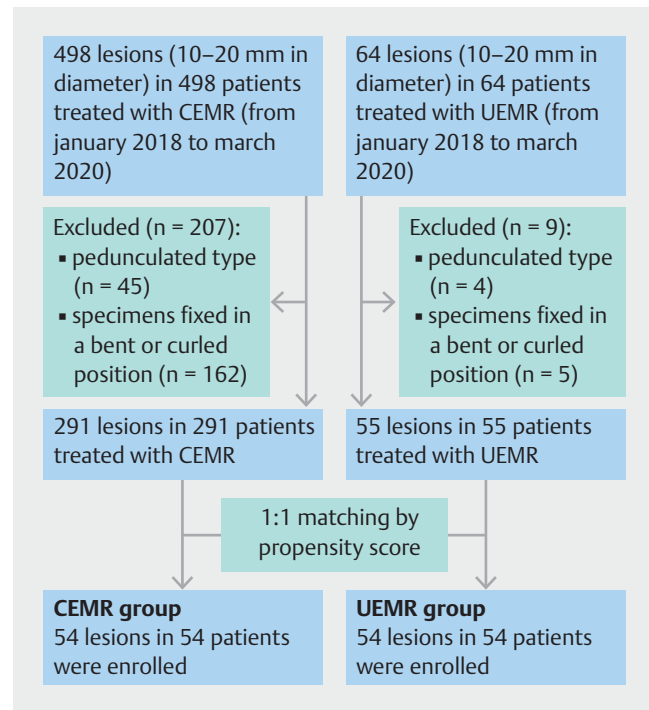
Results

► **Fig. 3** is a flowchart showing participant enrollment. Between January 2018 and March 2020, 64 patients with 64 colorectal lesions 10 to 20 mm in diameter underwent UEMR at our hospital. A total of nine lesions (four pedunculated lesions and five lesions in which the specimens were fixed in a bent or curled position) were excluded, and we enrolled the remaining 55 patients (55 lesions) and assigned them to the UEMR group. During the same period, 498 patients with 498 colorectal lesions 10 to 20 mm in diameter underwent CEMR. A total of 207 lesions (45 pedunculated lesions and 162 lesions in which the specimens were fixed in a bent or curled position) were excluded, and we enrolled the remaining 291 patients (291 lesions) and assigned them to the CEMR group.

The characteristics of patients and polyps before polypectomy in this study are shown in ► **Table 1**. Before PSM, there was no significant difference in sex, age, median tumor diameter, macroscopic type, or location between the UEMR and CEMR groups.

Fifty-four patients were selected for polypectomy in each group. The characteristics of the patients after polypectomy are summarized in ► **Table 2**. After polypectomy, there was no significant difference in sex, age, median tumor diameter, macroscopic type, or location between the UEMR and CEMR groups and baseline characteristics became balanced. In both groups, there were no residual lesions after ER and no cases in which treatment modality was converted from UEMR to CEMR.

After polypectomy, a comparison of the histopathological analysis between the UEMR and CEMR groups is shown in ► **Table 3**. The proportion of specimens containing SM tissue was 100% in both groups. The resection depths in the UEMR and CEMR groups are shown in ► **Fig. 4**. The median thickness of SM tissue was significantly greater in the CEMR group than in the UEMR group (1235 μm [95% CI, 1020–1530 μm] vs. 950 μm [95% CI, 830–1090 μm], respectively). However, vertical margins were negative in all lesions in both groups. There was no significant difference in horizontal margins, either unevaluable or positive, or histological types between the two groups.



► **Fig. 3** Flowchart of patient enrollment. CEMR, conventional endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection.

After PSM, a comparison of the procedure-related outcomes and adverse events between the UEMR and CEMR groups is shown in ► **Table 4**. The rates of en bloc resection and R0 resection in the UEMR versus the CEMR group were 91% (95% CI, [79.7%–96.9%]) vs. 93% (95% CI, [84.6%–98.8%]), and 87% (95% CI, [75.1%–94.6%]) vs. 89% (95% CI, [79.7%–96.9%]), respectively. There were no complications such as delayed postprocedural bleeding or perforation during the UEMR or CEMR procedure.

Discussion

To the best of our knowledge, this is the first study to evaluate and compare the resection depth achieved with UEMR and CEMR for the treatment of colorectal lesions using PSM. Occasionally, colorectal tumors without characteristics of deep submucosal invasion are found to be invasive upon pathological evaluation after ER. This study was not intended to verify the superiority of UEMR to CEMR; rather, it mainly aimed to consider the resection depth of UEMR, which has not been clarified. Our study showed that SM tissue was found in all cases in the UEMR group and that the median thickness of the SM tissue in the UEMR group was about 1000 μm , even though the resection depth achieved with UEMR was significantly more superficial than that achieved with CEMR.

Resection depth achieved using ER is a crucial factor in the curability of colorectal tumors. In Japan, intramucosal cancer or cancer with slight SM invasion (<1000 μm beyond the muscularis mucosae) is considered an indication for ER because

► **Table 1** Patient baseline characteristics before propensity score matching.

	CEMR group, n = 291		UEMR group, n = 55		P value
Sex, n (%)					
▪ Male	187	(64)	35	(64)	1.00
▪ Female	104	(36)	20	(36)	
Age, median (IQR), years	69 (61–74)		71 (65–75)		0.14
Lesion size, median (IQR), mm	12 (10–15)		12 (10–15)		0.13
Macroscopic type, n (%)					
▪ Superficial elevated	289	(99)	53	(96)	0.12
▪ Superficial depressed	2	(1)	2	(4)	
Location, n (%)					
▪ Cecum	31	(11)	12	(22)	0.07
▪ Ascending	76	(26)	11	(20)	
▪ Transverse	54	(19)	14	(25)	
▪ Descending	21	(7)	6	(11)	
▪ Sigmoid	73	(25)	8	(15)	
▪ Rectum	36	(12)	4	(7)	
CEMR, conventional endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection; IQR, interquartile range.					

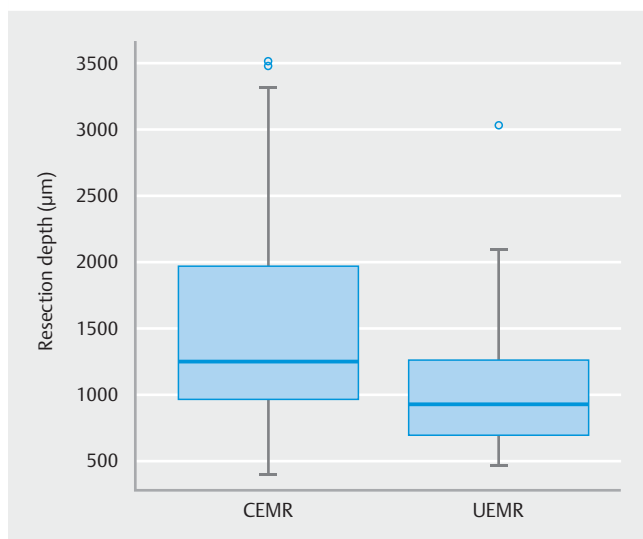
► **Table 2** Patient baseline characteristics in the CEMR group and UEMR group after propensity score matching.

	CEMR group n = 54		UEMR group n = 54		P value
Sex, n (%)					
▪ Male	37	(69)	34	(63)	0.69
▪ Female	17	(31)	20	(37)	
Age, median (IQR), years	67 (63–73)		71 (64–75)		0.14
Lesion size, median (IQR), mm	12 (10–15)		12 (10–15)		0.95
Macroscopic type, n (%)					
▪ Superficial elevated	53	(98)	53	(98)	1.00
▪ Superficial depressed	1	(2)	1	(2)	
Location, n (%)					
▪ Cecum	11	(20)	12	(22)	1.00
▪ Ascending	10	(19)	11	(20)	
▪ Transverse	14	(31)	14	(26)	
▪ Descending	7	(13)	6	(11)	
▪ Sigmoid	8	(15)	7	(13)	
▪ Rectum	4	(7)	4	(7)	
CEMR, conventional endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection; IQR, interquartile range.					

► **Table 3** Histopathological analysis in the CEMR group and UEMR group after propensity score matching.

	CEMR group n = 54		UEMR group n = 54		P value
Containing submucosal tissue, n (%) [95% CI]	54	(100) [93.4–100]	54	(100) [93.4–100]	1.00
The thickness of submucosal tissue, median (IQR), μm	1235 (970–1938)		950 (708–1325)		0.001
[95% CI]	[1020–1530]		[830–1090]		
Vertical margin unevaluable/positive, n (%) [95% CI]	0	(0) [0–6.6]	0	(0) [0–6.6]	1.00
Horizontal margin unevaluable/positive, n (%) [95% CI]	6	(11) [4.2–22.6]	7	(13) [5.4–24.9]	1.00
Histological type, n (%) [95% CI]					
▪ Hyperplastic polyp	2	(4) [0.5–12.7]	2	(4) [0.5–12.7]	0.52
▪ Sessile serrated lesion	9	(17) [7.9–29.3]	6	(11) [4.2–22.6]	
▪ Adenoma	39	(72) [58.4–83.5]	36	(67) [52.5–78.9]	
▪ Intramucosal adenocarcinoma	3	(6) [1.2–15.4]	8	(15) [6.6–27.1]	
▪ Submucosal adenocarcinoma	1	(2) [0–9.9]	2	(4) [0.5–12.7]	
▪ < 1,000 μm	1	(2) [0–9.9]	2	(4) [0.5–12.7]	
▪ \geq 1,000 μm	0	(0) [0–6.6]	0	(0) [0–6.6]	

CEMR, conventional endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection; CI, confidence interval; IQR, interquartile range.



► **Fig. 4** Box plot of the resection depth in the CEMR and UEMR groups. CEMR, conventional endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection.

there is no probability of lymph node metastasis [17]. SM deeply invasive cancer ($\geq 1000\mu\text{m}$ beyond the muscularis mucosae) is diagnosed on the basis of endoscopic findings such as fullness, erosion, ulceration, fold convergence, deformity, and rigidity, as well as image-enhanced endoscopy such as NBI or magnifying endoscopic observation [18–20]. Following con-

ventional white light imaging, all colorectal lesions were evaluated using M-NBI, which ruled out SM deeply invasive cancer in our study. Careful preresection optical assessment including M-NBI is required to ensure that only lesions with a low likelihood of containing SM deeply invasive cancer are treated with UEMR. With CEMR, SM injection lifts the submucosa and separates the mucosal layer from the muscle layer, and so the median thickness of SM tissue with CEMR was considered to be significantly greater than the median thickness of SM tissue with UEMR in the present study. However, the proportion of negative vertical margins was 100% with UEMR. Fukuda et al. reported that UEMR has a feasible no vertical margin involvement rate for resecting pathologically invasive CRC without characteristics of deep SM invasion [21]. If UEMR is performed for SM deeply invasive cancer, the possibility of vertical margin unevaluable/positive appears to be high. Our study has suggested that UEMR is indicated if there is no clear evidence of SM deeply invasive cancer on preoperative endoscopic diagnosis. Colorectal lesions in which there is the possibility of SM deeply invasive cancer may be suitable for resection by CEMR.

In a multicenter, randomized controlled trial, Yamashina et al. assessed the efficacy and safety of UEMR in comparison with CEMR on intermediate-sized colorectal polyps (10–20mm) and showed that the en bloc resection and R0 resection rates were significantly higher with UEMR compared with CEMR (89% vs. 75%, and 69% vs. 50%, respectively) [11]. For colorectal polyps 10 to 20mm in size, our study showed that the en bloc and R0 resection rates for UEMR were 91% and 87%, respectively. The en bloc resection rates in our UEMR group

► **Table 4** Procedure-related outcomes and adverse events in the CEMR group and UEMR group after propensity score matching.

	CEMR group, n = 54		UEMR group, n = 54		P value
	(95% CI)		(95% CI)		
En bloc resection, n (%) [95% CI]	50	(93) [84.6–98.8]	49	(91) [79.7–96.9]	0.73
R0 resection, n (%) [95% CI]	48	(89) [79.7–96.9]	47	(87) [75.1–94.6]	0.77
Procedure-related adverse events, n (%) [95% CI]					
▪ Delayed postprocedural bleeding	0	(0) [0–6.6]	0	(0) [0–6.6]	1.00
▪ Perforation	0	(0) [0–6.6]	0	(0) [0–6.6]	1.00

CEMR, conventional endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection; CI, confidence interval.

were similar to previously published results. In addition, there were no significant differences in the en bloc and R0 resection rates between UEMR and CEMR in our study. The reason for this may be the small sample size because this was a retrospective study performed in a single center. In addition, Yamashina et al. suggested in subset analysis that UEMR was better for lesions ≥ 15 mm ($P=0.016$). Because the median lesion size in both the CEMR and UEMR groups was smaller (12 mm) in our study, it is possible that the en bloc and R0 resection rates in our CEMR group was better and the difference between the two groups was not significant.

In the present study, there were no perforations and no cases of delayed bleeding in either group. Thus, there was no significant difference in the risk of delayed bleeding and perforation between UEMR and CEMR. Since 2012, there have been two cases of UEMR-related perforation [22, 23] and only one case of delayed perforation after UEMR [24], as described previously, whereas the CEMR perforation incidence range is 0% to 1.5% [11, 25, 26]. With UEMR, it is hypothesized that water immersion in a nondistended colon “floats” the mucosa and submucosa away from the deeper muscularis layer, thus mimicking the “cushion” effect of SM injection with CEMR [24]. Two multicenter prospective studies showed that the incidence of delayed bleeding with UEMR was 0% to 2.7% [11, 27]. The present study demonstrates that UEMR was not associated with an increased risk of adverse events such as delayed polypectomy bleeding or perforation compared with CEMR, as previously reported [28].

Knowing that SM lifting of certain polyps is sometimes technically difficult, UEMR might be a way to remove such lesions. Some studies have suggested that UEMR is indicated for recurrent and residual lesions of colorectal polyps and a superficial polyp located at the anastomosis after surgical colectomy [29, 30]. In addition, UEMR has also shown good results in resection of lesions at ileocecal valves and appendiceal orifices [31, 32]. With CEMR, the SM injection causes the borders of polyps to expand, thereby producing a larger defect after snare resection. With UEMR, floating of mucosa and submucosa over the muscularis layer leads to a change in the shape of the lesions, and some flat and sessile lesions become smaller and more polypoid in configuration [11, 33]. Resection of such lesions leads to smaller defects. Some studies have shown that fewer clips

are required after UEMR than after CEMR [34]. Furthermore, the avoidance of SM injection reduces the procedural costs associated with the use of injection needles. In addition, UEMR can be easily learned and performed by endoscopists experienced with CEMR and therefore be quickly adopted in a community practice [35].

This study had several limitations. First, this was a retrospective study performed in a single center. Second, we only evaluated the resection depth of representative specimens of the central part of the lesion, and so we did not assess the entire lesion. Because the center of almost all specimens had the greatest depth of resection, we evaluated the resection depth by using the thickest SM tissue in the area. Third, the selection of UEMR or CEMR was dependent on each endoscopist’s preference, thus the selection criteria for UEMR and CEMR for colorectal polyps could not be clarified in this retrospective study. Last, our sample size was too small to make conclusions about a definitive strategy. Because there are no previous data indicating the resection depth of UEMR and CEMR, we could not calculate an appropriate sample size to generate sufficient predictive power. In addition, the sample size was too small to evaluate histologic resection depth according to macroscopic tumor type and location. This pilot study should be positioned as the basis for a future multicenter prospective study.

Conclusions

In conclusion, our findings suggest that the median thickness of SM tissue in the UEMR group was about 1,000 μm . Although the resection depth achieved with UEMR was more superficial than that achieved with CEMR, UEMR may be a treatment option, especially for colorectal lesions ≤ 20 mm without suspicious findings of SM deeply invasive cancer. Prospective, randomized, multicenter studies involving larger numbers of individuals are needed to further investigate this issue.

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Competing interests

The authors declare that they have no conflict of interest.

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