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CLINICAL AT

Underwater vs Conventional Endoscopic Mucosal Resection of Large Sessile or Flat Colorectal Polyps: A Prospective Randomized Controlled Trial

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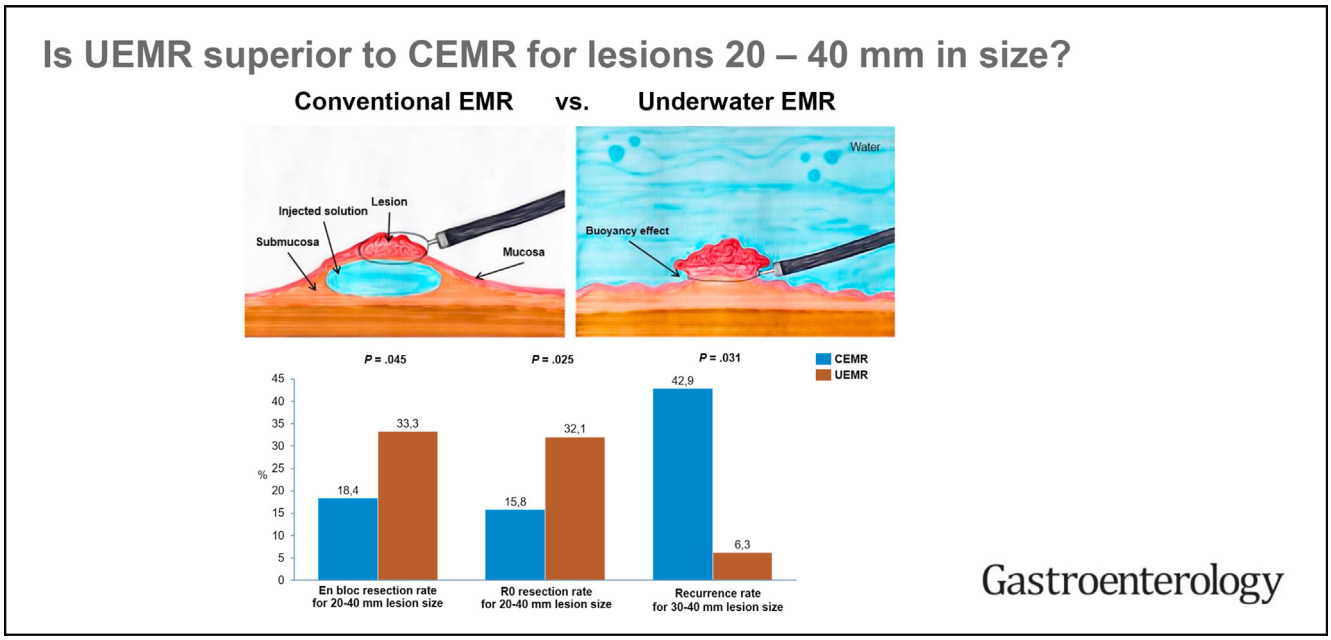

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BACKGROUND & AIMS: Conventional endoscopic mucosal resection (CEMR) with submucosal injection is the current standard for the resection of large, nonmalignant colorectal polyps. We investigated whether underwater endoscopic mucosal resection (UEMR) is superior to CEMR for large (20–40mm) sessile or flat colorectal polyps. **METHODS:** In this prospective randomized controlled study, patients with sessile or flat colorectal polyps between 20 and 40 mm in size were randomly assigned to UEMR or CEMR. The primary outcome was the recurrence rate after 6 months. Secondary outcomes included en bloc and R0 resection rates, number of resected pieces, procedure time, and adverse events. **RESULTS:** En bloc resection rates were 33.3% in the UEMR group and 18.4% in the CEMR group ($P = .045$); R0 resection rates were 32.1% and 15.8% for UEMR vs CEMR, respectively ($P = .025$). UEMR was performed with significantly fewer pieces compared to CEMR (2 pieces: 45.5% UEMR vs 17.7% CEMR; $P = .001$). The overall recurrence rate did not differ between both groups ($P = .253$); however, subgroup analysis showed a significant difference in favor of UEMR for lesions of >30 mm to ≤40 mm in size ($P = .031$). The resection time was significantly shorter in the UEMR group (8 vs 14 minutes; $P < .001$). Adverse events did not differ between both groups ($P = .611$). **CONCLUSIONS:** UEMR is superior to CEMR regarding en bloc resection, R0 resection, and procedure time for large colorectal lesions and shows significantly lower recurrence rates for lesions >30 mm to ≤40 mm in size. UEMR should be considered for the endoscopic resection of large colorectal polyps.

Keywords: Underwater; Conventional; Resection; Colonoscopy.

Abbreviations used in this paper: **CEMR, conventional endoscopic mucosal resection; CI, confidence interval; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ESGE, European society of gastroenterology; ITT, intention-to-treat; NBI, narrow-band imaging; OR, odds ratio; UEMR, underwater endoscopic mucosal resection.**

Most current article

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Conventional endoscopic mucosal resection (CEMR) is the current standard for the treatment of large colorectal polyps and has been shown to reduce colorectal cancer–related mortality.[1] The European Society of Gastroenterology (ESGE) recommends CEMR with submucosal injection for the resection of sessile or flat polyps of ≥10 mm in size.[2] However, one limitation of CEMR is its association with low en bloc resection rates, especially for polyps larger than 10 mm. Piecemeal resection is one of the main reasons for adenoma recurrence, with local recurrence rates of 15% to 30% on follow-up colonoscopy.[3–7] Endoscopic submucosal dissection (ESD), as an alternative approach, allows the en bloc resection of large polyps and has shown significantly lower recurrence rates compared to CEMR.[8–10] According to the ESGE guidelines, ESD should be considered for complex lesions with a high suspicion of submucosal invasion, such as 0-IIc or 0-IIa/0-IIc lesions, as well as nongranular-type lesions, larger than 2 cm, that may harbor superficial multifocal submucosal invasion.[11] However, ESD is not widely practiced in Western countries, because it is time-consuming, requires advanced skills and prolonged training, and is associated with higher complication rates compared to endoscopic mucosal resection (EMR), especially in the colon.[12,13]

For these reasons, an endoscopic resection technique superior to CEMR in terms of en bloc resection and local recurrence, but not at the expense of higher adverse events, is of paramount importance.

Underwater endoscopic mucosal resection (UEMR), first described by Binmoeller et al[14] in 2012, has emerged as an attractive alternative to CEMR for the resection of colorectal polyps. The concept of this technique is to immerse the polyp-bearing segment underwater and perform resection without submucosal lifting of the target lesion. During underwater colonic endosonography, it was observed that the mucosa and submucosa float away from the deeper muscle layer while the colonic muscularis propria remains circular with adequate distance to the lesion.[14] Several cohort studies have reported the safety and efficacy of this novel resection technique for colorectal polyps.[15,16] Five recent meta-analyses across a broad lesion size range have addressed the efficacy of UEMR in comparison to CEMR and have shown an overall superior en bloc resection rate for UEMR compared to CEMR.[17–21] However, these meta-analyses included studies of different designs, thereby diminishing the quality of evidence. One randomized controlled study has shown the superior efficacy of UEMR over CEMR regarding the R0 resection rate for colorectal polyps between 10 and 20 mm in diameter.[22] However, up until now, to our knowledge, there has been no published prospective randomized controlled trial to prove the advantage of UEMR over CEMR for colorectal polyps larger than 20 mm in diameter.

We conducted a randomized controlled trial to investigate whether UEMR is superior to CEMR for large sessile or flat colorectal polyps between 20 mm and 40 mm in size.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Conventional endoscopic mucosal resection (CEMR) with submucosal injection is the current standard for the resection of large, nonmalignant colorectal polyps. Underwater endoscopic mucosal resection (UEMR) has been shown to be more effective than CEMR with regard to the R0 resection rate for intermediate-size (10–20-mm) colorectal polyps.

NEW FINDINGS

In a randomized controlled trial, UEMR showed superiority to CEMR regarding en bloc resection, R0 resection, and procedure time for large colorectal polyps 20–40 mm in size and significantly decreased the recurrence rate for lesions >30 mm to ≤40 mm in size.

LIMITATIONS

Single-center trial.

IMPACT

The results recommend the use of UEMR over CEMR for the resection of large colorectal polyps up to 40 mm in size.

Methods

Study Design

This is a prospective randomized controlled study conducted at the University Hospital Augsburg in Augsburg, Germany. The clinical study was performed in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the medical ethics committee of the Ludwig-Maximilians University of Munich on August 24, 2017 (registration no. 17-456). The study protocol was not changed after trial commencement. All patients provided written informed consent before being included in the study.

Study Population and Polyps

Between August 2017 and October 2020, all adult patients (≥18 years) referred to our hospital for endoscopic mucosal resection (EMR) and who provided informed consent were enrolled for possible randomization.

Flat or sessile colorectal lesions, 20–40 mm in size, were eligible. Exclusion criteria included pregnancy, American Society of Anesthesiologists class III or higher, pedunculated lesions, residual lesions after endoscopic resection, familial polyposis syndrome, lesions in patients with inflammatory bowel disease, and lesions suspicious for deep submucosal invasion based on macroscopic appearance (narrow band imaging [NBI]) in magnifying endoscopy, as well as patients unwilling to provide written informed consent. During colonoscopy, all identified polyps underwent image documentation; in addition, the size, morphology, and location of each lesion were documented. The morphology of polyps was described according to the Paris classification.[23] Lesion size was measured with an open snare placed beside the polyp. Patients with multiple polyps meeting the inclusion criteria were also included.

Patients on antiplatelet agents or anticoagulants were asked to continue or discontinue their medication according to the ESGE guidelines.[24]

Endoscopic Procedure and Follow-Up

All CEMR procedures were performed by 6 experienced endoscopists, with an experience of at least 200 CEMRs. Two endoscopists performed the UEMR procedures and had an experience of at least 10 UEMRs before the trial was started. Each study patient received standardized bowel preparation before endoscopic resection, and patients received moderate sedation with midazolam and propofol for the procedure. All procedures were carried out with a high-definition video colonoscope (CF-HQ 190 video colonoscope, Olympus), and a distal transparent hood (Disposable Distal Attachment D-201-14304, Olympus America) was attached to the end of the endoscope to facilitate endoscopic observation and resection. After the cecum was reached, mucosal inspection was undertaken with CO_2 insufflation on endoscope withdrawal. Eligible polyps were randomly assigned to the UEMR or CEMR treatment group using a simple 1:1 randomization strategy. An opaque, sealed envelope containing a computer-generated randomization code with a serial number was opened by a research assistant before polyp resection. The research assistant was otherwise not involved in the clinical practice. All patients were blinded to the allocated treatment method during the endoscopic procedure. The allocation table was concealed from the endoscopists. For patients with more than 1 suitable polyp, each polyp was assigned to the UEMR or CEMR treatment group following the same randomization process described. The UEMR procedure included the following steps: insufflated CO_2 was completely removed, and the bowel lumen was filled with normal saline using a water jet pump (OFP-2, Olympus Medical System) until the lesion was totally immersed in water. The lesion and 2–3 mm of normal surrounding mucosa were subsequently resected using electrocautery (VIO 3, ERBE 5; Elektromedizin) with EndoCUT Q mode 2 and forced coagulation (Figure 1). The CEMR procedure included the following steps: normal saline solution was injected into the submucosa with a needle to lift the submucosal layer, the mucosal polyp-bearing protrusion was entrapped with a snare, and the polyp was resected using the same electrocautery settings as were used for UEMR. En bloc resection was intended in all lesions, but if not feasible, piecemeal EMR was performed with the allocated technique until the resection site was devoid of polypoid tissue. The choice of snare used for the resection was based on endoscopist's preference; snare size ranged from 15 to 25 mm (Supplementary Table 1).

The procedure time was measured by a second physician using the stopwatch of the endoscopy processor. Resected specimens were collected and placed in 10% formalin containers. After fixation, the entire lesion was cut into parallel pieces at intervals of 2–3 mm for subsequent histologic analysis.[25] After resection, prophylactic coagulation of vessels or clipping of the mucosal defect to prevent delayed bleeding or perforation was performed according to the endoscopist's preference. In the case of intraprocedural bleeding, hemoclips (HX-610-090/L, Olympus) or electrocoagulation with the snare tip (Soft Coagulation 3 or Spray Coagulation 3.5, VIO 3, ERBE 5; Elektromedizin) was performed.

Surveillance colonoscopy was performed 6 months after initial EMR. The resection scar was examined in the gas-distended colon, and biopsy samples of the resection scar were obtained to histologically confirm the absence of recurrence. When recurrent adenomatous tissue was detected at the

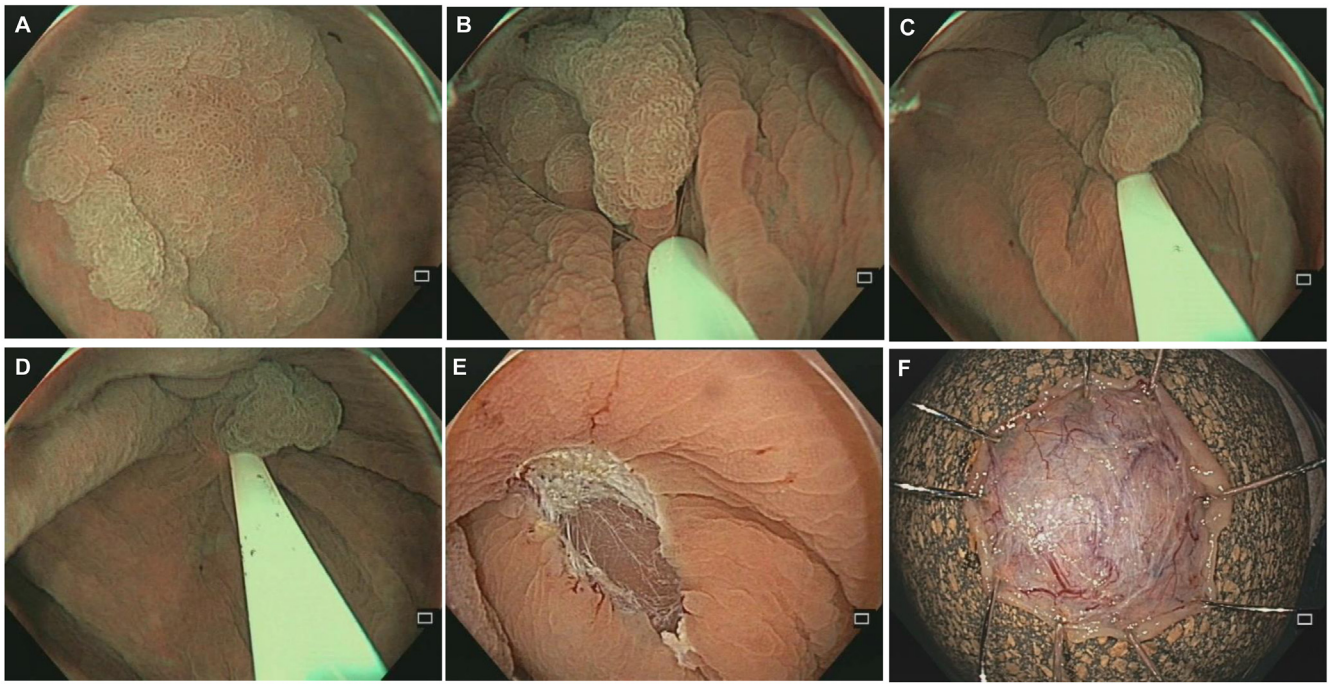

Figure 1. (UEMR. (*A*) NBI shows the underwater appearance of a lateral spreading tumor, granular type, approximately 20 mm in diameter. (*B–D*) NBI shows underwater lesion entrapment with a snare and underwater lesion resection. (*E*) White light endoscopy shows the wound after UEMR with no residual lesion. (*F*) The resected lesion.

resection site, the tissue was resected either with biopsy forceps or snare polypectomy until no residual tissue was left. The specimens were sent for subsequent histologic assessment to confirm recurrence.

Outcomes

The primary outcome was the difference in the recurrence rate after 6 months based on the macroscopic evaluation as well as the histologic assessment of the resection scar.

Secondary outcomes included the en bloc resection rate, R0 resection rate, number of snare resections needed to completely remove the lesion, procedure time, and adverse events.

En bloc resection was defined as 1-piece resection without any visible residual tissue on conventional white light imaging or NBI. R0 resection was defined as en bloc resection with histologically confirmed negative resection margins. Positive resection margins (R1) or unclear resection margins (RX) were referred to as non-R0 resection. The procedure time was defined as the period between the start of polyp immersion in normal saline (in the UEMR group) or submucosal injection (in the CEMR group) and completion of polyp resection. Adverse events included perforation or hemorrhage, requiring blood transfusion, endoscopic treatment, and/or surgery. Immediate hemorrhage was defined as continuous hemorrhage for $\geq$30 seconds immediately after polypectomy, but this was not considered as an adverse event. Overt bleeding within 14 days after UEMR or CEMR was defined as delayed hemorrhage. In addition, because patients were routinely monitored in the hospital for about 2 days after EMR, delayed bleeding was further subdivided into early ($\leq$48 hours after the procedure) and late (>48 hours after the procedure) phases. Intraprocedural perforation was defined as visual evidence of partially or completely interrupted muscle fibers on the wound base. Delayed perforation was defined as pneumoperitoneum or ascites on abdominal computed tomography with or without signs of peritonitis within 14 days after resection. Patients were asked to communicate adverse events within 2 weeks after the procedure.

Subgroup analyses were conducted regarding the location of the lesion, morphology (flat or sessile), polyp histology, and size of the lesion ($\geq$20 mm and $\leq$30 mm or >30 mm and $\leq$40mm). The learning curve for UEMR during the trial was analyzed by subdividing the study period into 2 time periods and evaluating the en bloc resection rate in each period.

Sample Size

Based on previous studies showing a recurrence rate of 20% to 40% after piecemeal resection vs 3% after en bloc resection and based on reports of higher en bloc resection rates after UEMR vs CEMR, we hypothesized that UEMR would be superior to CEMR regarding recurrence rates on follow-up after 6 months. We estimated a recurrence rate of 30% and 10% for CEMR and UEMR, respectively. To achieve 80% power detecting a 20% difference between the 2 groups, we calculated a sample size of 72 for each group. Assuming a loss to follow-up rate of approximately 10%, the target sample size was set at 158 in total. The recurrence rate of UEMR was assumed to be 30% of that of the CEMR group under the null hypothesis and 10% under the alternative hypothesis. A 2-sided Fisher exact test was used as the statistical test. The statistical level was set at 0.05 as the threshold for statistical significance.

Statistical Analysis

All statistical analyses were carried out using SPSS, version 25.0 (SPSS, Chicago, IL) and were performed in the full analysis set, which included all randomized polyps. The primary and secondary outcomes were analyzed according to the intention-to-treat (ITT) principle. Categorical outcomes were analyzed using the Fisher exact test and were expressed as percentages. Continuous outcomes were compared using the Mann-Whitney *U* test and were presented as mean ± standard deviation or median (interquartile range). Preplanned subgroup analyses were conducted based on the described method. A *P* value of <.05 (2-sided) was considered statistically significant.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Baseline Data and Clinical Characteristics

A total of 266 patients were recruited and underwent colonoscopy between August 2017 and October 2020. In total, 158 polyps from 147 patients were eligible and underwent randomization. Recruitment ended when the number of polyps had reached the predetermined number. UEMR was not performed in 1 patient because the lesion was identified as carcinoma on macroscopic appearance. For ITT analysis of the primary endpoint, 81 polyps were assigned to the UEMR group and 76 polyps to the CEMR group. Of these, 3 polyps in the CEMR group were excluded because of protocol violation (2 recurrent polyps and 1 patient with consent withdrawal). Among those in the UEMR group, 1 recurrent lesion was excluded, and 5 polyps were excluded because of crossover to the CEMR group because of visibility impairment as a result of intraprocedural bleeding after the first en bloc UEMR attempt. Finally, 148 polyps (75 in the UEMR group and 73 in the CEMR group) were included in the per-protocol analysis. A flowchart of patient enrollment is shown in Supplementary Figure 1.

Baseline demographic and clinical characteristics of the patients, lesions, and procedures between both groups are presented in Table 1. The mean age of study patients was 67.2 years (standard deviation, 10.8), 65.7% were male, and 36.9% of patients were on antithrombotic or anticoagulant treatment. The median polyp size was 25 mm. Among the 157 polyps, 74.4% were located in the right colon, and 52.2% of colonic polyps were tubular adenomas. Overall, 21.8% of polyps were classified as 0-Is and 65.6% as 0-IIa types. Prophylactic clip closure of the resection wounds was performed in 34.6% of lesions in the UEMR group and 52.6% in the CEMR group. Both treatment arms were comparable with regard to polyp location, size, morphology, and histopathology, as well as clinical and demographic characteristics.

Table 1. Baseline Characteristics of the Study Participants, Lesions, and Procedures

Characteristics	CEMR Group (n = 76)	UEMR Group (n = 81)	*P* Value
Age, *y*			
Mean (SD)	66.3 (11.9)	68.1 (9.6)	
Median (range)	68 (38–91)	68 (33–85)	.481[a]
Sex, (n/total) %			
Male	(52/76) 68.4	(51/81) 63.0	
Female	(24/76) 31.6	(30/81) 37.0	.472[b]
Antithrombotics used, (n/total) %			
Aspirin	(16/76) 21.1	(18/81) 22.2	>.999[b]
Antiplatelet	(5/76) 6.6	(4/81) 4.9	.740[b]
Anticoagulants	(7/76) 9.2	(8/81) 9.9	>.999[b]
None	(51/76) 67.1	(54/81) 66.7	>.999[b]
Lesion size, *mm*			
Mean (SD)	28.1 (6.6)	27.8 (6.2)	
Median (range)	30 (20–40)	25 (20–40)	.850[a]
Lesion size, *mm*, (n/total) %			
20	(19/76) 25.0	(20/81) 24.7	
25	(18/76) 23.7	(22/81) 27.2	
30	(23/76) 30.3	(19/81) 23.5	
35	(5/76) 6.6	(14/81) 17.3	
40	(11/76) 14.5	(6/81) 7.4	.176[b]
Location, (n/total) %			
Cecum	(19/76) 25.0	(20/81) 24.7	
Ascending	(29/76) 38.2	(28/81) 34.6	
Right flexure	(6/76) 7.9	(15/81) 18.5	
Transverse	(9/76) 11.8	(7/81) 8.6	
Descending	(8/76) 10.5	(5/81) 6.2	
Sigmoid	(4/76) 5.3	(6/81) 7.4	
Rectum	(1/76) 1.3	(0/81) 0	.409[b]
Morphology, (n/total) %			
0-Is	(20/76) 26.3	(14/81) 17.3	
0-IIa	(49/76) 64.5	(54/81) 66.7	
0-IIb	(2/76) 2.6	(3/81) 3.7	
0-IIc	(1/76) 1.3	(0/81) 0	
0-IIa/0-IIc	(1/76) 1.3	(0/81) 0	
0-IIa/0-Is	(3/76) 3.9	(10/81) 12.3	.169[b]
Histology, (n/total) %			
Tubular	(38/76) 50.0	(44/81) 54.3	
Tubulovillous	(17/76) 22.4	(19/81) 23.5	
Villous	(1/76) 1.3	(0/81) 0	
Sessile serrated adenoma	(19/76) 25.6	(16/81) 19.8	
Adenocarcinoma	(0/76) 0	(1/81) 1.2	
Hyperplastic polyp	(0/76) 0	(1/81) 1.2	
Marginal zone lymphoma	(1/76) 1.3	(0/81) 0	.402[b]
Operator, (n/total) %			
A	(24/76) 31.6	(54/81) 66.7	
B	(23/76) 30.3	(27/81) 33.3	
C	(5/76) 6.6	(0/81) 0	
D	(6/76) 7.9	(0/81) 0	
E	(7/76) 9.2	(0/81) 0	
F	(11/76) 14.5	(0/81) 0	<.001[b]
Prophylactic clipping, (n/total) %	(40/76) 52.6	(28/81) 34.6	.076[b]
Intraprocedural bleeding, (n/total) %	(11/76) 14.5	(19/76) 23.5	.162[b]
Hospital stay, *days*			
Mean (SD)	2.8 (2.8)	3.1 (3.8)	
Median (range)	2.0 (1–26)	2.0 (1–26)	.933[a]

SD, standard deviation.
[a]Mann-Whitney *U* test.
[b]Fisher exact test.

Primary Outcomes

Primary and secondary outcomes are presented in Table 2. A total of 118 patients (75.2%) underwent surveillance colonoscopy after a median follow-up of 6 months (range, 5–8 months). All cases with macroscopic evidence of local recurrence were also confirmed histopathologically. Overall recurrence rate was 15.1% in the UEMR group and 24.6% in the CEMR group ($P = .253$). The recurrence rates for lesions of >30 mm to ≤40 mm in size were 6.3% and 42.9% for UEMR and CEMR, respectively ($P = .031$). All local recurrent lesions were successfully treated with en bloc or piecemeal resection. Histopathologic diagnoses of recurrent lesions were consistent with the histopathology of the initial lesion.

Secondary Outcomes

The en bloc resection and R0 resection rates in the UEMR group were significantly higher than those in the CEMR group: 33.3% vs 18.4% ($P = .045$) and 32.1% vs 15.8% ($P = .025$), respectively. The superior en bloc and R0 resection rates of UEMR were driven by the subgroup of polyps with a diameter of ≥20 mm to ≤30 mm.

In the case of piecemeal resection, UEMR was performed with significantly fewer snare resections (2 pieces: 45.5% vs 17.7%; $P = .001$). UEMR was performed significantly faster than CEMR (8 vs 14 minutes, respectively; $P < .001$).

The PP analysis supported the ITT analysis for recurrence rate, en bloc resection rate, R0 resection rate, piecemeal resection rate, and procedure time.

Adverse Events

Adverse events are presented in Table 3. Intraprocedural bleeding was observed in 19 procedures (23.5%) in the UEMR group and 11 (14.5%) in the CEMR group ($P = .162$). UEMR was continued in 14 (73.7%) procedures after bleeding had been controlled conventionally using coagulation forceps. UEMR had to be terminated and resection continued with CEMR in 5 procedures (26.3%). All intraprocedural bleedings were managed conservatively and did not require transfusion, surgery, or interventional radiology. Delayed bleeding within 48 hours after polyp resection occurred in 1 patient in the UEMR group and 2 patients in the CEMR group ($P = .611$); endoscopic hemostasis with clip closure or coagulation forceps was required in all 3 cases. No case of late delayed (>48 hours) bleeding was communicated by any patient after hospital discharge. No perforation was observed in any of the cases. There were no intra- or postprocedural perforations in either group. Overall, adverse events were not statistically different between the 2 groups.

Subgroup Analyses

Subgroup analyses are shown in Table 4. With regard to the learning curve, there was no difference in the en bloc UEMR resection rates between the first and second time periods of the study (48.1% vs 51.9%, respectively; $P = .816$). Primary and secondary outcomes did not differ among the endoscopists within each treatment arm and between both treatment arms. Odds ratios (ORs) for UEMR en bloc and R0 resection for tubular adenoma and Paris 0-IIa lesions were 2.14 (95% confidence interval [CI], 1.14–4.04) and 2.18 (95% CI, 1.23–3.87), respectively (Figures 2 and 3).

Discussion

To our knowledge, this is the first randomized controlled clinical trial to compare the effectiveness and safety of UEMR with CEMR for large colorectal polyps between 20 and 40 mm in size.

CEMR is well established and currently the treatment modality of choice for the resection of large colorectal polyps up to 20 mm in size.[2,25–27] However, the major drawback of CEMR is its low rate of en bloc resection, especially for lesions >20 mm in size, because en bloc resection rates decrease with an increase in polyp size.[28,29] Piecemeal resection is regarded as an independent risk factor for local recurrence in up to 15%–50%.[4,30,31]

In a multicenter randomized controlled trial, Yamashina et al[22] were able to show superior en bloc and R0 resection rates for UEMR compared to CEMR for intermediate-size (10–20 mm) sessile colorectal polyps. A multicenter prospective study by Rodríguez Sànchez et al[15] reported en bloc resection rates of 62% vs 49% for UEMR vs CEMR, respectively, in polyps with an average size of 20.78 mm. Yen et al[32] found no difference in incomplete resection rates for UEMR and CEMR for colorectal lesions >10 mm in size.

Several meta-analyses have reported the superior outcomes of UEMR over CEMR regarding en bloc resection rates,[18–21] which is refuted in the most recent meta-analysis by Chandan et al[17] for polyps >20 mm in size. However, the generalizability of these results can be questioned because different study designs were included in these meta-analyses. In our randomized controlled trial, we found that UEMR is associated with a significantly higher en bloc and R0 resection rate compared with CEMR for large sessile and flat colorectal lesions without an increased risk for adverse events. These results might be attributed to the natural magnification effect under water, which improves the delineation of the borders of the lesions as well as the detection of residual neoplastic tissue after resection.[32] During UEMR, lesions float into the water-filled lumen, whereas the underlying muscularis propria retains its circular configuration.[14,33] Water immersion results in less distension of the bowel lumen compared with gas insufflation and prevents large lesions from further extending over the colonic wall. Thus, even much larger lesions can be entrapped with standard-sized snares and are more amenable to en bloc resection. This phenomenon seems to be more significant in larger lesions.[34,35] In contrast, air insufflation and submucosal injection during CEMR often stretch the size of the lesions and flatten the target lesion, resulting in impaired lesion margin delineation, snare slipping, and snare capture of the entire lesion.[36] This may adversely affect the success of en bloc resection and increase the number of resections needed to completely remove a polyp. Consistent with this observation, we found

Table 2. Primary and Secondary Outcomes

Parameter	CEMR	UEMR	*P* Value
ITT analysis	n = 76	n = 81	
En bloc resection, *mm*, (n/total) %			
Overall (↔)	(14/76) 18.4	(27/81) 33.3	.045[b]
≤30	—	(24/61) 39.3	.057[b]
>30 (↕)	—	(3/20) 15.0	
≤30	(14/60) 23.3	—	.033[b]
>30 (↕)	(0/16) 0	—	
≤30 (↔)	(14/60) 23.3	(24/61) 39.3	.078[b]
>30 (↔)	(0/16) 0	(3/20) 15.0	.238[b]
Piecemeal resection, (n/total) % (↔)	(62/76) 81.6	(54/81) 66.7	.045[b]
Piecemeal resection, (n/total) %			
2 pieces (↔)	(11/62) 17.7	(25/54) 45.5	
≥3 pieces (↔)	(51/62) 82.3	(29/54) 54.5	.001[b]
R0 resection, *mm*, (n/total) %			
Overall (↔)	(12/76) 15.8	(26/81) 32.1	.025[b]
≤30	—	(23/61) 37.7	.096[b]
>30 (↕)	—	(3/20) 15.0	
≤30	(12/60) 20.0	—	
>30 (↕)	(0/16) 0	—	.060[b]
≤30 (↔)	(12/60) 20.0	(23/61) 37.7	.045[b]
>30 (↔)	(0/16) 0	(3/20) 15.0	.238[b]
6-month follow-up, (n/total) % (range, 5–8 months) (↔)	(65/76) 85.5	(53/81) 65.4	.007[b]
Recurrence, *mm*, (n/total) %			
Overall (↔)	(16/65) 24.6	(8/53) 15.1	.253[b]
≤30	—	(7/37) 18.9	
>30 (↕)	—	(1/16) 6.3	.410[b]
≤30	(10/51) 19.6	—	
>30 (↕)	(6/14) 42.9	—	.090[b]
≤30 (↔)	(10/51) 19.6	(7/37) 18.9	>.999[b]
>30 (↔)	(6/14) 42.9	(1/16) 6.3	.031[b]
Procedure time, *min*			
Mean (SD) (↔)	18.4 (14.778)	10.9 (9.820)	
Median (IQR) (↔)	14 (2–75)	8 (1–42)	<.001[a]
Per-protocol analysis	n = 73	n = 75	
En bloc resection, *mm*, (n/total) %			
Overall (↔)	(14/73) 19.2	(27/75) 36.0	.028[b]
≤30	—	(24/57) 42.1	
>30 (↕)	—	(3/18) 16.7	.089[b]
≤30	(14/58) 24.1	—	
>30 (↕)	(0/15) 0	—	.059[b]
≤30 (↔)	(14/58) 24.1	(24/57) 42.1	.049[b]
>30 (↔)	(0/15) 0	(3/18) 16.7	.233[b]
Piecemeal resection, (n/total) % (↔)	(59/73) 80.8	(48/75) 64.0	.028[b]
Piecemeal resection, (n/total) %			
2 pieces (↔)	(11/59) 18.6	(25/48) 52.1	
≥3 pieces (↔)	(48/59) 81.4	(23/48) 47.9	.001[b]
R0 resection, *mm*, (n/total) %			
Overall (↔)	(12/73) 16.4	(26/75) 34.7	.011[b]
≤30	—	(23/57) 40.4	
>30 (↕)	—	(3/18) 16.7	.090[b]
≤30	(12/58) 20.7	—	
>30 (↕)	(0/15) 0	—	.061[b]
≤30 (↔)	(12/58) 20.7	(23/57) 40.4	.027[b]
>30 (↔)	(0/15) 0	(3/18) 16.7	.233[b]
6-month follow-up, (n/total) % (range: 5–8 months) (↔)	(64/73) 87.6	(50/75) 66.7	.003[b]

Table 2. Continued

Parameter	CEMR	UEMR	*P* Value
Recurrence, (n/total) %			
Overall (↔)	(15/64) 23.4	(8/50) 16.0	.357[b]
≤30	—	(7/36) 19.4	
>30 (↕)	—	(1/14) 7.1	.414[b]
≤30	(9/51) 17.6	—	
>30 (↕)	(6/13) 46.2	—	.061[b]
≤30 (↔)	(9/51) 17.6	(7/36) 19.4	>.999[b]
>30 (↔)	(6/13) 46.2	(1/14) 7.1	.033[b]
Procedure time, *min*			
Mean (SD) (↔)	18.23 (14.98)	9.94 (9.30)	
Median (IQR) (↔)	13 (7–25)	7 (3–13)	.003[a]

NOTE. ↔ indicates the difference between CEMR and UEMR; ↕ indicates the difference within the CEMR or UEMR group. IQR, interquartile range; SD, standard deviation.
[a]Mann-Whitney *U* test.
[b]Fisher exact test.

that whenever en bloc resection was not achieved in the UEMR group, in most cases, only a minimal residual lesion was left and was subsequently removed entirely with another snare capture. Thus, when the en bloc resection rate and the 2-pieces resection rate were taken together, UEMR achieved a complete resection rate of 64%. Sakamoto et al[37] found that the removal of 5 or more pieces constitutes an independent risk factor for local recurrence after piecemeal EMR. Thus, UEMR allows the resection of even large colonic polyps with a minimum of pieces.

For UEMR, circumferential marking of the lesion was not performed routinely. However, this could be a method to improve the visibility of the tumor margins during resection and thereby even improve the en bloc and R0 resection rates.

The higher en bloc and R0 resection rates of UEMR over CEMR were mainly driven by the subgroup of polyps with a diameter of ≥20 mm to ≤30 mm in size and might be limited to this size. As an alternative approach, ESD shows higher en bloc and R0 resection rates of 91% and 82.9%,[12] respectively, as well as low recurrence rates of approximately 2%[38] for large colorectal polyps. Therefore, ESD should always be considered, especially for complex lesions with a high suspicion of submucosal invasion. However, ESD has a flat learning curve and, especially in the colon, can be associated with perforation rates between 1.4% and 14%.[12,28,39–41] Despite longer procedure times, colorectal ESD is safe, especially in institutions where it is performed routinely. In non-Asian countries, the performance level of colorectal ESD is gradually improving; however, the en bloc and R0 resection rates and the complication rates remain significantly behind those in most Asian countries.[12,42]

Several studies suggest that piecemeal resection increases the risk of local recurrence.[6,43] This is clinically important because more frequent surveillance colonoscopies are required to avoid the development of interval cancers. We speculated that the advantage of superior en bloc resection rates of UEMR over CEMR likely translates into lower recurrence rates on follow-up colonoscopy. A systematic review found that local recurrence after endoscopic en bloc resection of nonpedunculated colorectal lesions occurs in 3% and in 20% for piecemeal EMR, and more than 90% of recurrences are detected 6 months after EMR.[6] In addition to piecemeal resection, needle tract seeding during submucosal injection in CEMR can also contribute to higher recurrence rates.[44,45] A recent article as well as the current ESGE guidelines recommend endoscopic follow-up within 3–6 months after piecemeal resection for polyps larger than 20 mm.[46,47] Our primary endpoint, which was the recurrence rate after 6 months, was evaluated macroscopically and histopathologically using biopsy samples taken from the resection scar. We observed a difference in patient attendance to the 6-month follow-up colonoscopies between the 2 groups. However, we do not believe that this difference influenced the recurrence rate because we compared the difference in proportions between both groups and not the absolute differences. Consistent with higher rates of en bloc resection, several meta-analyses have shown that UEMR was associated with significantly lower rates of residual or recurrent polyps at surveillance colonoscopy.[18,20,21] In our study, we did not find a significant difference in overall recurrence rate between the 2 groups; however, we found a significantly lower recurrence rate for lesions >30 mm to ≤40 mm in size in the UEMR group. This

Table 3. Adverse Events

Parameter	CEMR Group, (n/total) %	UEMR Group, (n/total) %	*P* Value
Delayed bleeding			
<48 hours	(2/76) 2.6	(1/81) 1.2	
>48 hours	(0/76) 0	(0/81) 0	.611[a]
Intraprocedural perforation	(0/76) 0	(0/81) 0	>.999[a]
Delayed perforation	(0/76) 0	(0/81) 0	>.999[a]

[a]Fisher exact test.

Table 4. Subgroup Analyses

Parameter	CEMR Group, (n/total) %	UEMR Group, (n/total) %	*P* Value
En bloc resection			
First time period	—	(13/27) 48.1	
Second time period (↕)	—	(14/27) 51.9	.816[a]
En bloc resection of UEMR operators		Total n = 81	
A	—	(20/54) 37.0	
B (↕)	—	(7/27) 25.9	.454[a]
En bloc resection of CEMR operators	Total n = 76		
A	(5/24) 20.8		
B	(8/23) 34.8		
C	(0/5) 0		
D	(0/6) 0		
E	(1/7) 14.3		
F (↕)	(0/11) 0	—	.131[a]
En bloc resection of CEMR and UEMR operators			
A (↔)	(5/24) 20.8	(20/54) 37.0	.195[a]
B (↔)	(8/23) 34.8	(7/27) 25.9	.548[a]
R0 resection of UEMR operators		Total n = 81	
A	—	(19/54) 35.2	
B (↕)	—	(7/27) 25.9	.292[a]
R0 resection of CEMR operators	Total n = 76		
A	(4/24) 17.4		
B	(7/23) 31.8		
C	(0/5) 0		
D	(0/6) 0		
E	(1/7) 14.3		
F (↕)	(0/11) 0	—	.202[a]
R0 resection of CEMR and UEMR operators			
A (↔)	(4/24) 17.4	(19/54) 35.2	.115[a]
B (↔)	(7/23) 31.8	(7/27) 25.9	.761[a]
Recurrence of UEMR operators		Total n = 53	
A	—	(6/39) 15.4	
B (↕)	—	(2/14) 14.3	>.999[a]
Recurrence of CEMR operators	Total n = 65		
A	(4/20) 20.0		
B	(5/19) 26.3		
C	(0/4) 0		
D	(3/5) 60.0		
E	(1/7) 14.3		
F (↕)	(3/10) 30.0	—	.417[a]
Recurrence of CEMR and UEMR operators			
A (↔)	(4/20) 20.0	(6/39) 15.4	.721[a]
B (↔)	(5/19) 26.3	(2/14) 14.3	.670[a]
En bloc resection of UEMR polyp histologies		Total n = 81	
Adenocarcinoma		(0/1) 0	
Hyperplastic polyp		(1/1) 100.0	
SSA		(6/16) 37.5	
Tubular		(14/44) 31.8	
Tubulovillous (↕)	—	(6/19) 31.6	.721[a]
En bloc resection of CEMR polyp histologies	Total n = 76		
Marginal zone lymphoma	(1/1) 100.0		
SSA	(6/19) 31.6		
Tubular	(6/38) 15.8		
Tubulovillous	(1/17) 5.9		
Villous (↕)	(0/1) 0	—	.083[a]

Table 4. Continued

Parameter	CEMR Group, (n/total) %	UEMR Group, (n/total) %	*P* Value
En bloc resection of CEMR and UEMR polyp histologies			
SSA (↔)	(6/19) 31.6	(6/16) 37.5	.736[a]
Tubular (↔)	(6/38) 15.8	(14/44) 31.8	.123[a]
Tubulovillous (↔)	(1/17) 5.9	(6/19) 31.6	.092[a]
R0 resection of UEMR polyp histologies		Total n = 81	
Adenocarcinoma		(0/1) 0	
Hyperplastic polyp		(1/1) 100.0	.408[a]
SSA		(6/16) 37.5	
Tubular		(14/44) 31.8	
Tubulovillous (↕)	—	(5/19) 26.3	
R0 resection of CEMR polyp histologies	Total n = 76		
Marginal zone lymphoma	(1/1) 100.0		
SSA	(6/19) 31.6		
Tubular	(4/38) 10.5		
Tubulovillous	(1/17) 5.9		
Villous (↕)	(0/1) 0	—	.05[a]
R0 resection of CEMR and UEMR polyp histologies			
SSA (↔)	(6/19) 31.6	(6/16) 37.5	.736[a]
Tubular (↔)	(4/38) 10.5	(14/44) 31.8	.031[a]
Tubulovillous (↔)	(1/17) 5.9	(5/19) 26.3	.182[a]
En bloc resection of UEMR polyp morphologies		Total n = 81	
0-Is		(5/14) 35.7	
0-IIa		(17/54) 31.5	
0-IIb		(1/3) 33.3	
0-IIa/0-Is (↕)	—	(4/10) 40.0	.915[a]
En bloc resection of CEMR polyp morphologies	Total n = 76		
0-Is	(4/20) 20.0		
0-IIa	(8/49) 16.3		
0-IIb	(1/2) 50.0		
0-IIc	(0/1) 0		
0-IIa/0-IIc	(1/1) 100.0		
0-IIa/0-Is (↕)	(0/3) 0	—	.264[a]
En bloc resection of CEMR and UEMR polyp morphologies			
0-Is (↔)	(4/20) 20.0	(5/14) 35.7	.435[a]
0-IIa (↔)	(8/49) 16.3	(17/54) 31.5	.107[a]
0-IIb (↔)	(1/2) 50.0	(1/3) 33.3	>.999[a]
0-IIa/0-Is (↔)	(0/3) 0	(4/10) 40.0	.497[a]
En bloc resection of UEMR polyp localizations		Total n = 81	
Cecum		(9/20) 45.0	
Ascending		(9/28) 32.1	
Right flexure		(6/15) 40.0	
Transverse		(2/7) 28.6	
Descending		(0/5) 0	
Sigmoid		(1/6) 16.7	
Rectum (↕)	—	—	.5[a]
En bloc resection of CEMR polyp localizations	Total n = 76		
Cecum	(2/19) 10.5		
Ascending	(4/29) 13.8		
Right flexure	(2/6) 33.3		
Transverse	(3/9) 33.3		
Descending	(3/8) 37.5		
Sigmoid	(0/4) 0		
Rectum (↕)	(0/1) 0	—	.357[a]

Table 4. Continued

Parameter	CEMR Group, (n/total) %	UEMR Group, (n/total) %	*P* Value
En bloc resection of CEMR and UEMR polyp localizations			
Cecum (↔)	(2/19) 10.5	(9/20) 45.0	.031[a]
Ascending (↔)	(4/29) 13.8	(9/28) 32.1	.123[a]
Right flexure (↔)	(2/6) 33.3	(6/15) 40.0	>.999[a]
Transverse (↔)	(3/9) 33.3	(2/7) 28.6	>.999[a]
Descending (↔)	(3/8) 37.5	(0/5) 0	.231[a]
Sigmoid (↔)	(0/4) 0	(1/6) 16.7	>.999[a]
Rectum	(0/1) 0	—	—

NOTE. Operators A and B performed UEMR, and operators A–F performed CEMR. ↔ indicates the difference between CEMR and UEMR; ↕ indicates the difference within the CEMR or UEMR group.
[a]Fisher exact test.

result might be attributable to the fact that UEMR allows the resection of even large colonic polyps with a minimum of pieces. Despite a lower recurrence rate for lesions >30 mm to ≤40 mm in size compared to CEMR, the recurrence rate of UEMR is still considerably higher than ESD.[38] Endoscopists faced with the task of colorectal polyp resection need to critically weigh the risk of recurrence after resection against the risk of submucosal invasion for each polyp.

Lesion size[5] and histology of adenoma[31,48] have been reported to be risk factors for local recurrence. A prospective trial devised a polyp grading system, which related the outcome of CEMR to morphology, polyp size, and polyp access.[49,50] Our subgroup analyses suggest that for UEMR, en bloc and R0 resections were superior for tubular adenoma and Paris 0-IIa lesions and showed an overall trend toward superior en bloc and R0 resection irrespective of lesion size, polyp morphology, histology, or polyp location.

CEMR is often considered to be technically challenging in the right hemicolon, especially in the cecum, because of more difficult scope operability and a possible higher risk of perforation. In our study, we found no lesion to be particularly difficult with UEMR. In fact, UEMR has been shown to be feasible and effective even in lesions at the ileocecal valve and appendiceal orifice,[51,52] as well as for recurrent or residual lesions, where submucosal lifting is often suboptimal because of submucosal fibrosis.[53]

In our study, we investigated the learning curve of both endoscopists by dividing patients undergoing UEMR procedures into a first and second time period. The aim was to find out if improvements in UEMR techniques during the trial might contribute to better en bloc resection rates. Consistent with the findings of several studies, which have shown that endoscopists skilled in CEMR easily adopt UEMR without specific training[54–56] and that the learning curve for CEMR often plateaus at 100 cases,[57] we found no statistically significant difference regarding the en bloc resection rate between patients undergoing UEMR in the 2 time periods of the study.

Even though operator A performed more procedures than operator B, an internal evaluation of the performance of both operators showed that this did not affect the overall outcome of the study. Furthermore, even though it became obvious that UEMR was easy to learn, the number of operators performing UEMR, which was determined in the study protocol, was not changed in the course of the study.

UEMR can be performed significantly faster than CEMR because endoscopists can skip the step of submucosal injection. Submucosal injection involves finding the correct submucosal plane for injection, which usually requires more than 1 injection. Also, interchanging the needle and the snare repeatedly may be more time consuming than the process of water submersion of the polyp-bearing colonic segment during UEMR. In addition, submucosal injection expands the mucosa and artificially enlarges the diameter of the lesion.

In this study, intraprocedural bleeding was observed in 19 (23.5%) procedures in the UEMR group and 11 (14.5%) in the CEMR group, all of which could be managed using hemoclips or coagulation forceps. Intraprocedural bleeding is not considered a complication; however, it interrupts and prolongs the resection procedure. It has been reported to be an important risk factor for local recurrence, because the concern about control of intraprocedural bleeding distracts the endoscopist from his or her primary focus of removing all visible residual adenoma.[50,58] In 14 (73.7%) procedures, UEMR was continued after bleeding had been controlled. UEMR had to be terminated and resection continued with CEMR in only 5 procedures (26.3%). Hence, intraprocedural severe bleeding during UEMR is rare, and bleeding control is possible with conventional methods, after which UEMR can be continued. A switch from UEMR to CEMR because of intraprocedural bleeding is usually not necessary. In CEMR, needle puncture for submucosal injection might precipitate bleeding. Large studies reported postprocedural bleeding rates after CEMR of 6% for lesions of >20 mm.[59] Lesions of >30 mm (OR, 2.5; 95% CI, 1.5–4.2), proximal colon location (OR, 2.3; 95% CI, 1.4–4.0), or any major comorbidity (OR, 1.5; 95% CI, 0.9–2.6) have been identified as risk factors.[60] Prophylactic use of clips seems to decrease delayed bleeding rates.[61] In our study, postprocedural bleeding occurred in only 1 case in the UEMR group and 2 cases in the CEMR group. These findings are consistent with previous reports.[22,32,62]

In this trial, no perforation occurred in either group. Submucosal injection in CEMR creates a cushion between the polyp and the muscularis layer, preventing perforation.

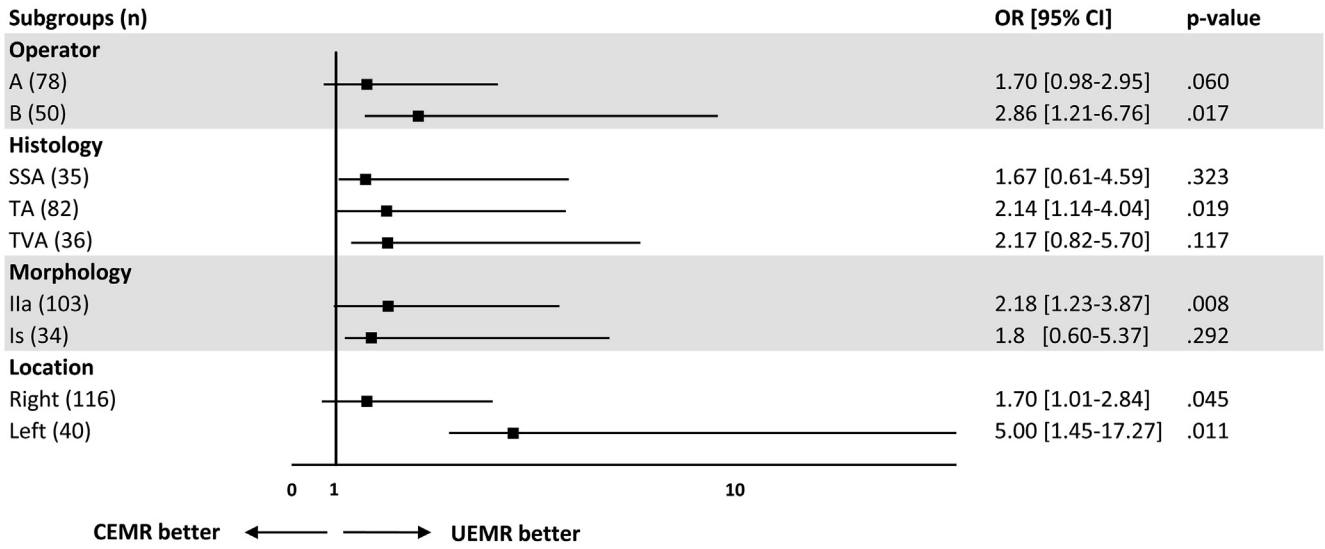

Figure 2. Subset analyses for en bloc resection. SSA, sessile serrated adenoma; TA, tubular adenoma; TVA, tubulovillous adenoma.

In UEMR, the cushion effect is mimicked by the buoyancy effect. To date, only 1 perforation during UEMR, which occurred in a retroflexed position in the right hemicolon, has been reported.[63] Overall, UEMR results in similar adverse events compared to CEMR and, therefore, can be performed safely without the need for submucosal injection.

Our study may have several limitations. First, endoscopists could not be blinded to the group allocation, raising some concerns for bias. However, this is a problem that cannot be solved in randomized controlled trials investigating endoscopic techniques. Second, lesion size was estimated macroscopically, but it is known that endoscopists usually overestimate polyp size by as much as 20%, especially when the lesion is larger than 1 cm.[64–66] To overcome this limitation, lesion size was measured with an opened snare. Third, all patients remained in the hospital for a minimum of 48 hours after the procedure; adverse events within this time were systematically monitored. We did not systematically monitor patients after discharge from the hospital. However, patients were asked to contact the hospital and report any adverse event that occurred after hospital discharge. Therefore, late delayed bleeding or perforation (>48 hours) might be underestimated in our study. Fourth, 5 polyps in the UEMR group crossed over to the CEMR group because of intraprocedural bleeding after the first en bloc UEMR attempt. We emphasize that these cases were excluded from the per-protocol analysis. Fifth, this is a single-center trial, and it may be unclear whether these results can be extrapolated to other institutions. However, 6 experienced operators participated in our trial, and no differences regarding primary or secondary

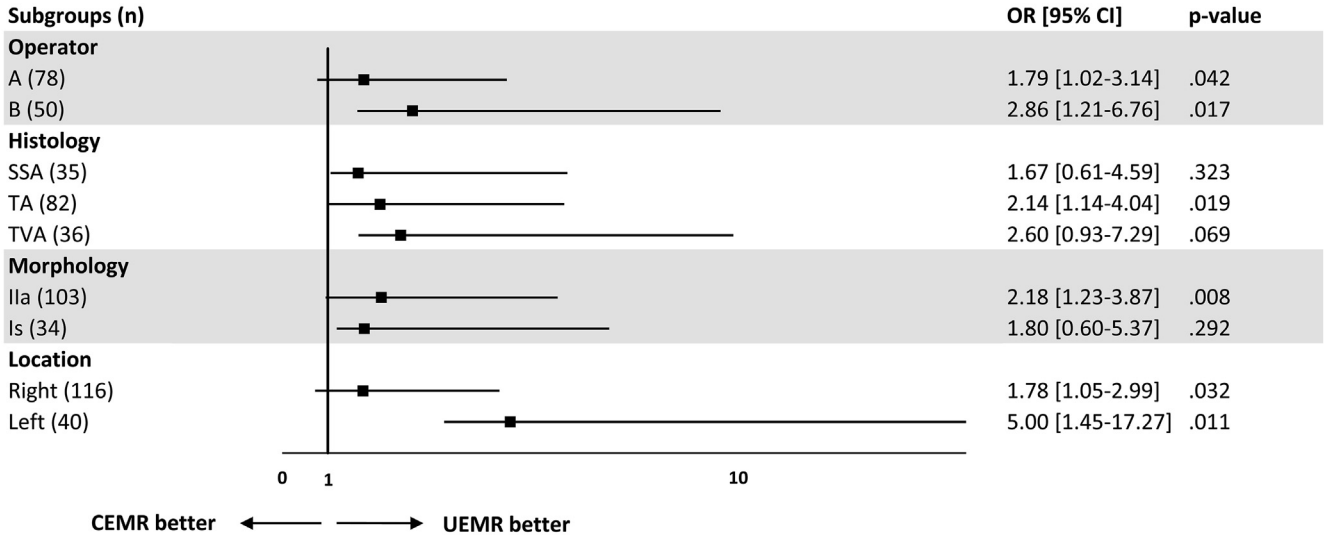

Figure 3. Subset analyses for R0 resection.

outcomes were observed among the operators. Thus, we assume the generalizability of our results.

In conclusion, our randomized controlled study has shown that UEMR is superior to CEMR regarding en bloc resection, R0 resection, and procedure time in the treatment of large colorectal polyps (20–40 mm). Although the en bloc and R0 resection rates of UEMR were superior to those of CEMR, especially for lesions between 20 and 30 mm in size, the overall en bloc and R0 resection rates remain below the en bloc and R0 resection rates achieved by ESD. However, compared with CEMR, UEMR significantly reduces the recurrence rate for polyps >30 mm to ≤40 mm in size and can be performed with significantly fewer pieces. UEMR is safe, quick, and easy to learn. Therefore, considering the balance between risks and benefits, we consider UEMR to be an ideal technique for the resection of large benign colorectal polyps up to 40 mm in size. In contrast, large polyps with suspicion of submucosal invasion should be treated by ESD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.07.044.

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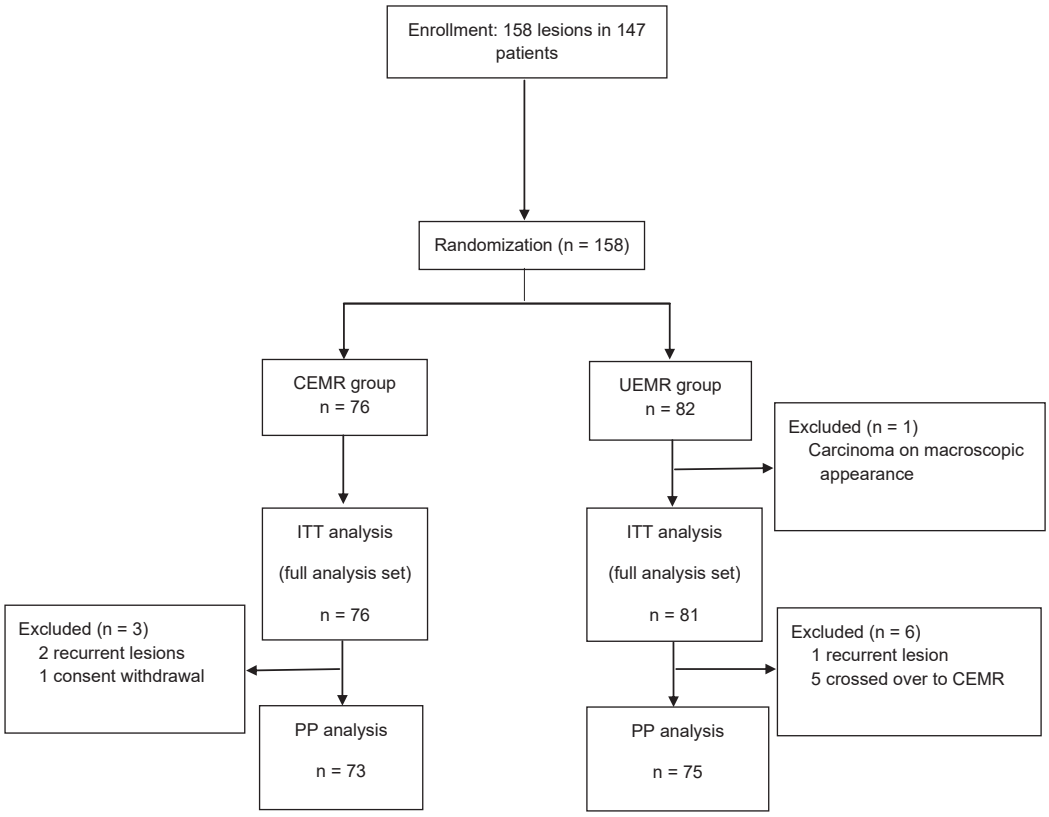
Conflicts of interest
This author discloses the following: Helmut Messmann reports relationships with the following endoscopic companies: Apollo Endosurgery, Biogen, Boston Scientific, CDx Diagnostic, Cook Medical, CSL Behring, Dr Falk Pharma, Endo Tools Therapeutics, Erbe, Fujifilm, Hitachi, Janssen-Cilag, Medwork, Norgine, Nutricia, Olympus, Ovesco Endoscopy, Servier Deutschland, and US Endoscopy; has received grants from Amgen, Bayer, Dr. Falk Pharma, MSD, Novartis Olympus, and Roche; has received honoraria from Covidien, Dr Falk Pharma, and Olympus; and has received consultation fees from Boston Scientific, CDx Diagnostics, Covidien, Erbe, Lumendi, Norgine, and Olympus. The remaining authors disclose no conflicts.



Supplementary Figure 1. Flow diagram of the study. PP, per protocol.

Supplementary Table 1. Types of Snares Used in This Study

HF polyp snare, 15 mm, monofilament, SD-990-15, Meiners Medizintechnik
HF polyp snare, 25 mm, monofilament, SD-990-25, Meiners Medizintechnik
Snare Master, 20 mm, SD-210U-15, Olympus Medical Systems
Snare Master, 25 mm, SD-210U-25, Olympus Medical Systems