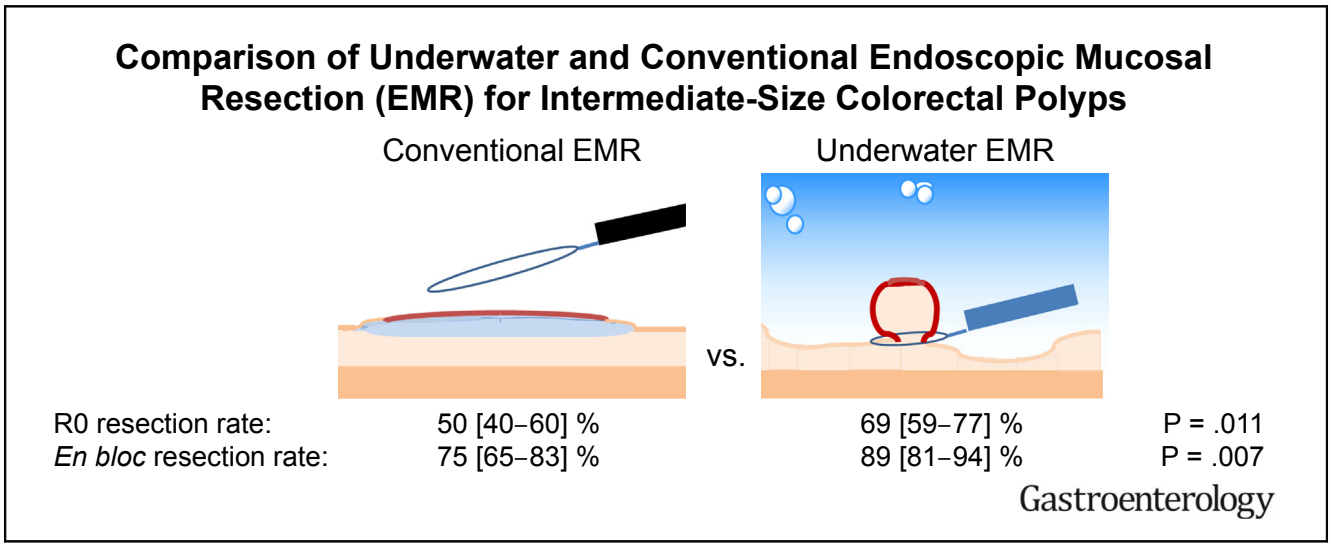
Gastroenterology 2019;157:451–461

Comparison of Underwater vs Conventional Endoscopic Mucosal Resection of Intermediate-Size Colorectal Polyps

Takeshi Yamashina,[1,2] Noriya Uedo,[1] Tomofumi Akasaka,[1,3] Taro Iwatsubo,[1] Yasuki Nakatani,[4] Takuji Akamatsu,[4] Takuji Kawamura,[5] Yoji Takeuchi,[1] Shigehiko Fujii,[6] Toshihiro Kusaka,[6] and Toshio Shimokawa[7]

[1]Department of Gastrointestinal Oncology, Osaka International Cancer Institute, Osaka, Japan; [2]Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Osaka, Japan; [3]Department of Gastroenterology and Hepatology, National Hospital Organization, Osaka National Hospital, Osaka, Japan; [4]Department of Gastroenterology and Hepatology, Japanese Red Cross Society Wakayama Medical Center, Wakayama, Japan; [5]Department of Gastroenterology, Kyoto Second Red Cross Hospital, Kyoto, Japan; [6]Department of Gastroenterology and Hepatology, Kyoto Katsura Hospital, Kyoto, Japan; and [7]Department of Clinical Study Support Center, Wakayama Medical University, Wakayama, Japan



BACKGROUND & AIMS: Endoscopic mucosal resection (EMR) with submucosal injection is an established method for removing colorectal polyps, although the en bloc resection rate decreases when polyp size exceeds 10 mm. Piecemeal resection increases local recurrence. Underwater EMR (UEMR) is an effective technique for removal of sessile colorectal polyps and we investigated whether it is superior to conventional EMR (CEMR). **METHODS:** We conducted a multicenter randomized controlled trial at 5 institutions in Japan. Patients with endoscopically diagnosed, intermediate-size (10–20 mm) sessile colorectal lesions were randomly assigned to undergo UEMR or CEMR. Only the most proximal lesion was registered. The UEMR procedure included immersion of the entire lumen in water and snare resection of the lesion without submucosal injection of normal saline. We analyzed outcomes of 108 colorectal lesions in the UEMR group and 102 lesions in the CEMR group. R0 resection was defined as en bloc resection with a histologically confirmed negative resection margin. The primary endpoint was the difference in the R0 resection rates between groups. **RESULTS:** The proportions of R0 resections were 69% (95% confidence interval [CI] 59%–77%) in the UEMR group vs 50% (95% CI 40%–60%) in the CEMR group ($P = .011$). The proportions of en bloc resections were 89% (95% CI 81%–94%) in the UEMR group vs 75% (95% CI 65%–83%) in the CEMR group ($P = .007$). There was no significant difference in median procedure time (165 vs 175 seconds) or proportions of patients with adverse events (2.8% in the UEMR group vs 2.0% in the CEMR group). **CONCLUSIONS:** In a multicenter randomized controlled trial, we found that UEMR significantly increased the proportions of R0 resections for 10- to 20-mm sessile colorectal lesions without increasing adverse events or procedure time. Use of this procedure should be encouraged. Trials registry number: UMIN000018989

Keywords: Colon; Endoscopy; Large; Efficacy.

Abbreviations used in this paper: **CEMR, conventional EMR; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ITT, intention-to-treat; LST-NG, non–granular-type, laterally spreading tumor; UEMR, underwater EMR.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.04.005

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Endoscopic mucosal resection (EMR) with submucosal injection is performed to remove colorectal polyps, although the en bloc resection rate decreases when polyp size exceeds 10 mm. Underwater EMR is an effective technique for removal of sessile colorectal polyps.

NEW FINDINGS

In a multicenter randomized controlled trial, underwater EMR significantly increased the proportions of R0 resections for 10- to 20-mm sessile colorectal lesions without increasing adverse events or procedure time.

LIMITATIONS

Endoscopists were not blinded to the procedure they performed, and there was no long-term follow-up data on recurrence.

IMPACT

The results recommend use of underwater EMR over CEMR for endoscopic removal of intermediate-size (10–20 mm) colorectal polyps.

Colorectal cancer is the third most common cancer in men and the second most common in women.[1] In 2018, among the 1.8 million patients worldwide with newly diagnosed colorectal cancer, 881,000 died of the disease.[2–4]

Endoscopic resection of colorectal polyps has been shown to reduce colorectal-cancer–related mortality,[5] and endoscopic mucosal resection (EMR) is an established method for removing advanced (>10 mm) sessile colorectal polyps. The en bloc resection rate decreases (<77%), however, when the polyp size exceeds 10 mm.[6,7] The resulting high local recurrence rate (>15%) after piecemeal resection is clinically problematic.[6–8] Although endoscopic submucosal dissection (ESD) allows en bloc resection of large polyps,[9,10] this technique requires advanced skill, has a longer procedure time, and is more costly than EMR. Hence, it is not widely practiced globally. Recently, underwater EMR (UEMR) has emerged as an alternative to conventional EMR (CEMR) and is reported to be effective for removing flat or large colorectal polyps.[11] With UEMR, the bowel lumen is filled with water instead of air/CO_2, and the lesion is captured and resected with a snare without submucosal injection of normal saline. Although several cohort studies have indicated the efficacy of UEMR,[12–15] there has been no prospective comparative randomized study to prove its advantage over CEMR. Therefore, we conducted a multicenter randomized controlled trial to investigate the effectiveness of UEMR compared with CEMR for endoscopic removal of intermediate-size (10–20 mm) sessile colorectal lesions.

Methods

Study Design

This prospective, multicenter randomized controlled trial involved 5 Japanese institutions: Osaka International Cancer Institute (Institution A); Osaka Red Cross Hospital (Institution B); Japanese Red Cross Society Wakayama Medical Center (Institution C); Kyoto Second Red Cross Hospital (Institution D); and Kyoto Katsura Hospital (Institution E). The trial complied with the Declaration of Helsinki, and the study protocol (No. 1505296059) was approved on August 11, 2015, by the Institutional Review Board of Osaka Medical Center for Cancer and Cardiovascular Diseases (lately, Osaka International Cancer Institute) and each participating institution. The study was registered in the University Hospital Medical Network Clinical Trials Registry as UMIN000018989. The manuscript was prepared according to the Consolidated Standards of Reporting Trials 2010 Statement.[16] All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Eligibility criteria included patients aged ≥20 years undergoing endoscopic resection for colorectal mucosal lesions (adenoma, intramucosal adenocarcinoma, or sessile serrated adenoma/polyp) that were 10 to 20 mm in diameter. The endoscopic diagnosis of mucosal lesions was based on their macroscopic appearance,[17,18] findings on narrow-band imaging, or the pit pattern classification in magnifying chromoendoscopy. Endoscopic resection was indicated for lesions with Narrow-band Imaging International Colorectal Endoscopic classification Type 1 with expanded crypt openings and/or thick and branched vessels,[19] or Type 2,[20] and/or Kudo classification Type II with an open crypt,[21] Type III or IV,[22] or selected cases of irregular V_I (slightly irregular V_I[23] or irregular V_I without a demarcation line[24]). 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 (10–26 mm).

Exclusion criteria included pedunculated lesions; residual lesions after endoscopic resection; and lesions in patients with inflammatory bowel disease, familial polyposis, electrolyte abnormality, coagulopathy, or severe organ failure. All patients were checked as to whether they were taking an antithrombotic agent. They also underwent various laboratory tests, including complete blood count, blood chemistry tests (alanine aminotransferase, alkaline phosphatase, aspartate transaminase, bilirubin, albumin, blood urea nitrogen, creatinine, sodium, potassium, and chloride); prothrombin time and international normalized ratio; chest radiography; and electrocardiography. For patients undergoing antithrombotic treatment, whether to continue was determined according to the Japanese Guidelines for Gastroenterological Endoscopy.[25,26]

In patients with multiple lesions, only 1 lesion per patient was registered to maintain the independence and distribution for the units of analysis. To avoid operator selection bias for a lesion treated with UEMR or CEMR, we chose the most proximal lesion that fulfilled the inclusion criteria as the object of study.

All patients provided written informed consent after receiving an explanation of the endoscopic procedures and study participation.

Operators

Expert endoscopists were certified by the Japan Gastroenterological Endoscopy Society and had at least 10 years'

experience in endoscopic therapy. Nonexpert endoscopists had <10 years' experience in endoscopic treatment.

Endoscopic Procedure

All procedures were carried out with a high-definition RGB sequential video-endoscopy system (EVIS LUCERA ELITE; Olympus Medical Systems, Tokyo, Japan). In both groups, it was left to the endoscopist's preference whether a cap was used or scope insertion was carried out underwater or in air/CO_2. After cecal intubation, mucosal observation was undertaken with air/CO_2 insufflation in all patients. When a target lesion was found, it was removed by UEMR or CEMR. All endoscopists attempted en bloc resection at the initial resection. At each institution, the electrosurgical unit and settings were determined according to the availability of the machines. The UEMR procedure included the following: (1) complete deflation of the colorectal lumen; (2) total immersion of the lesion in normal saline using a mechanical water pump (OFP-2: Olympus Medical Systems); (3) snaring the lesion and the surrounding mucosa; and (4) resection using electrocautery (Endo-cut or pulse cut mode) (Figure 1, Video 1).[14] 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. After endoscopic resection, the edge of the resection wound was carefully examined. If a remnant lesion was apparent or suspected, it was resected using the same method until complete removal was achieved. The polypectomy snares used for both methods were chosen depending on availability in each institution. Resected wounds were closed with clips according to operator's preference.

Before this randomized controlled trial commenced, a preliminary single-arm study was conducted from October 2015 to January 2016 in 20 patients at Institutions A and B to confirm the safety and efficacy of UEMR. Videos of the UEMR procedures during the preliminary study were then used to explain the procedure to endoscopists at Institutions C to E.

Histological Examination

After resection, the specimens were retrieved, immersed in 10% formalin, and sent to the Department of Pathology in each institution for histological assessment. Histological diagnosis of the lesion and involvement of the resection margin were evaluated according to the Japanese Classification of Colorectal Carcinoma.[27]

Randomization and Masking

Random numbers were generated using computer software (Excel 2016; Microsoft Corp., Redmond, WA). A research assistant who was not involved in clinical practice randomly assigned eligible patients in a 1:1 ratio to the UEMR or CEMR group, using a minimization method[28] after stratification by the

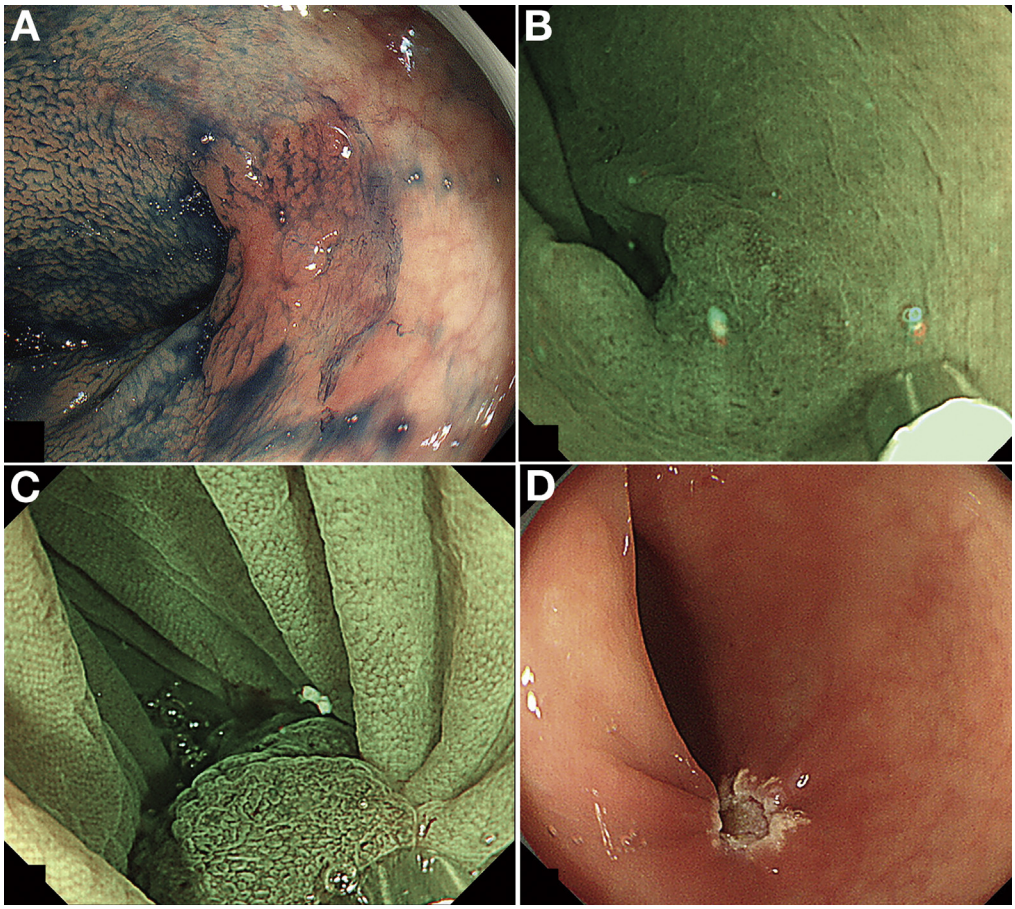


Figure 1. (*A*) White light endoscopy shows a lateral spreading tumor, nongranular type, approximately 15 mm in diameter in the sigmoid colon. (*B*) Narrow-band imaging (NBI) shows underwater appearance of the same lesion. (*C*) NBI shows underwater resection with a snare. (*D*) White light endoscopy shows the wound after underwater EMR with no residual lesion.

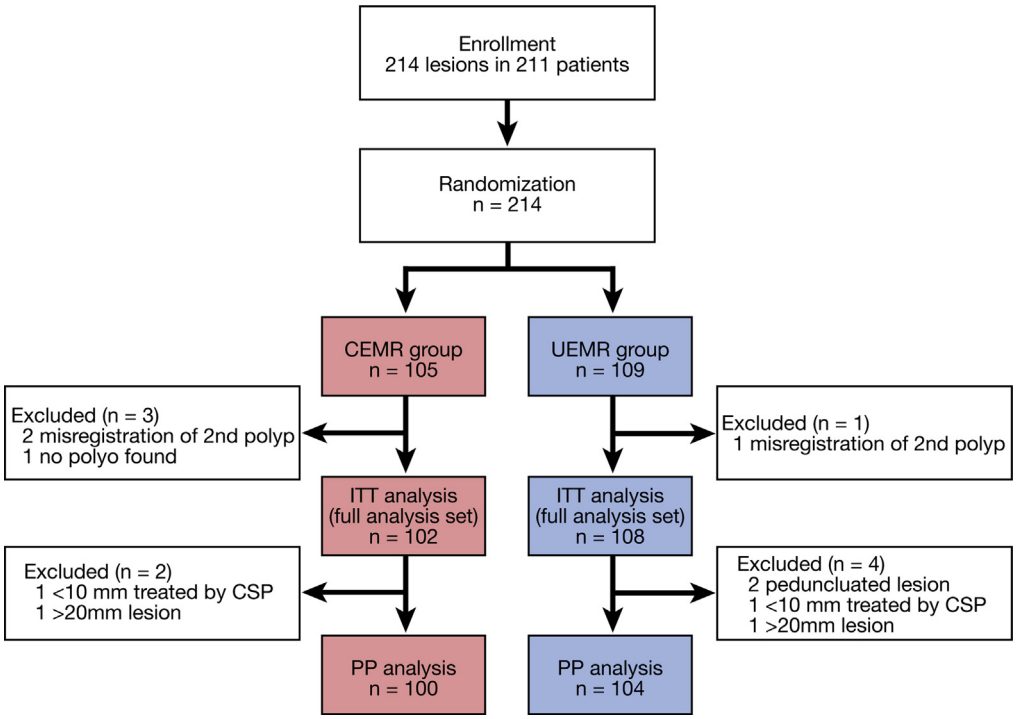


Figure 2. Flow diagram of the study. CSP, cold snare polypectomy; PP, per protocol.

operators' experience and institutions. The research assistant informed the operator of the treatment allocated just before the endoscopic procedure. The allocation table was concealed from the operators. Patients were masked for the allocated treatment method during the endoscopic procedures.

Outcomes

The primary endpoint in this study was the difference in R0 resection rates between the UEMR and CEMR groups. Secondary endpoints included the en bloc resection rate, procedure time, and adverse events. En bloc resection was defined as endoscopically assessed removal of the lesion in one piece. R0 resection was defined as en bloc resection with a histologically confirmed negative resection margin. Non-R0 resection included a positive resection margin (R1) or an unclear/indeterminate resection margin (RX). The procedure time in the UEMR group was measured from the start of immersion in normal saline from the endoscope until complete removal of the polyp. The procedure time in the CEMR group was measured from insertion of the injection needle until complete removal of the polyp. Adverse events (perforation, hemorrhage, or hyponatremia) were graded according to the Common Toxicity Criteria for Adverse Events 4.03.[29] Perforation during the procedure was defined as visible peritoneal fat on the endoscopic image and/or evidence of air or luminal contents outside the gastrointestinal tract[30] on abdominal computed tomography. Intraprocedural hemorrhage was not regarded as an adverse event if it was managed by endoscopic hemostasis. Postoperative hemorrhage was defined as overt bleeding within 14 days after UEMR or CEMR, requiring endoscopic hemostasis, and it was divided into early ($\leq$48 hours after the procedure) and late (>48 hours after the procedure) phases. Emergency colonoscopy was indicated for patients with 2 or more episodes of moderate-to-marked hematochezia, a decrease in the hemoglobin level of $\geq$2 g/dL, and/or unstable circulatory dynamics. All adverse events were verified by patient interview 2 weeks after the procedure.

A subset analysis was performed regarding the location of the lesion (right side, left side, or rectum), morphology (sessile or superficial), size of the lesion (<15 or $\geq$15 mm), at which institution it was removed (A/B or C–E), and the operator's experience (expert or nonexpert).

Sample Size

We hypothesized that UEMR would be superior to CEMR for endoscopic R0 resection of colorectal polyps. Previous studies reported that the CEMR R0 resection rate for colorectal polyps >20 mm was 33% to 57%.[6,31,32] We therefore estimated that the R0 resection rate for CEMR for intermediate-size (10–20 mm) colorectal polyps would be 50%, and then assumed that UEMR could increase the R0 resection rate to 70%. The required sample size of 103 for each group achieved 80% power to detect a 20% difference between the groups. The R0 resection rate of UEMR was assumed to be 50% of that of the CEMR group under the null hypothesis and 70% under the alternative hypothesis. The statistical test used was the 2-sided Fisher's exact test with a significance level of .05. Therefore, we planned to enroll 210 patients, taking into consideration the possibility of some dropouts.

Statistical Analysis

The primary endpoint was analyzed according to the intention-to-treat (ITT) principle. We analyzed categorical outcomes using Fisher's exact test and compared continuous outcomes using the Mann–Whitney U test. Odds ratios were calculated using logistic regression analysis. $P < .05$ (2-sided)

Table 1. Baseline Characteristics of the Study Subjects and Procedures in This Study

Characteristic	CEMR group (n = 102)	UEMR group (n = 108)
Sex, male/female	75/27	64/44
Median age, *yr* (range)	68 (42–95)	70 (43–86)
Antithrombotics used, n (%)		
Antiplatelet	11 (10)	6 (6)
Anticoagulant	4 (4)	7 (6)
Antiplatelet and anticoagulant	1 (1)	1 (1)
None	86 (85)	94 (87)
Hospitalization, n (%)		
Yes	99 (97)	106 (98)
No	3 (2.9)	2 (1.9)
Location, n (%)		
Cecum	15 (15)	16 (15)
Ascending	25 (25)	21 (19)
Transverse	28 (27)	29 (27)
Descending	8 (7.8)	11 (10)
Sigmoid	17 (17)	23 (21)
Rectum	9 (8.8)	8 (7.4)
Morphology, n (%)		
Superficial elevated	58 (57)	64 (59)
Superficial depressed	0	1 (0.9)
Protruded sessile	44 (43)	41 (38)
Pedunculated	0	2 (1.9)
Median lesion size, *mm* (range)	13.5 (7–25)	14 (7–25)
Lesions treated, n (%)		
1	25 (25)	24 (22)
2	24 (24)	17 (16)
3	19 (19)	16 (15)
>4	34 (33)	51 (47)
Institution, n (%)		
A	52 (51)	54 (50)
B	33 (32)	35 (32)
C	9 (8.9)	10 (9.3)
D	6 (5.9)	6 (5.6)
E	2 (2)	3 (2.8)
Operators' experience, n (%)		
Expert	53 (52)	57 (53)
Nonexpert	49 (48)	51 (47)
Use of cap, n (%)		
Yes	99 (97)	106 (98)
No	1 (1)	1 (1)
Unknown	2 (2)	1 (1)
Insufflation		
Air	33 (32)	44 (41)
CO_2	69 (68)	64 (59)
Prophylactic clipping		
Yes	59 (58)	76 (70)
No	43 (42)	32 (30)

was considered to indicate significance. Multiple comparisons in the subset analysis were corrected with Bonferroni's method. All statistical analyses were carried out using R version 3.5.1 software (www.r-project.org).

Results

Endoscopic Procedures and Equipment

Altogether, 10 expert and 18 nonexpert operators participated in this study. The operators' detailed experience is shown in Supplementary Table 1. High-definition video-colonoscopes, caps, electrosurgical units and settings, and snares used in this study are shown in Supplementary Tables 2 to 5. All procedures in the UEMR group were performed with a video-endoscope equipped with water jet function and 200 to 400 mL of normal saline was usually infused in each patient.

Participant Flow

From February 2016 to December 2017, we enrolled 211 patients with 214 colorectal lesions and randomly assigned them to the UEMR group (n = 109) or CEMR group (n = 105). Subsequently, CEMR was not performed in 1 patient because the lesion was not identified. In 1 patient in the UEMR group and 2 in the CEMR group, 2 lesions were misregistered because of unfamiliarity of the research assistant and endoscopists with the study protocol at the beginning of the study. Thus, 210 patients with 210 colorectal lesions (108 in the UEMR group and 102 in the CEMR group) were finally included in the ITT analysis for the primary endpoint. Four patients in the UEMR group and 2 in the CEMR group were excluded because of protocol violation (2 pedunculated polyps), and misestimation of the polyp size (2 polyps <10 mm treated by cold snare polypectomy and 2 lesions >20 mm), leaving 204 patients (104 in the UEMR group and 100 in the CEMR group) in the per-protocol analysis (Figure 2).

Baseline Data

Baseline characteristics of the patients, lesions, and procedures are shown in Table 1. Institution and operator experience, which were used as preadjustment factors, were similar between the 2 groups. Altogether, 14 patients in the UEMR group and 16 in the CEMR group took antithrombotic drugs (Supplementary Table 6). Most patients (98% in the UEMR group and 97% in the CEMR group) were hospitalized as a standard of care in Japan. A cap was used for most procedures (98% in the UEMR group and 97% in the CEMR group). Prophylactic clip closure of the resection wounds was performed in 70% of the UEMR patients and 58% of the CEMR patients.

Procedure-related Outcomes

The R0 resection rate (95% confidence interval) in the UEMR group was significantly higher than that in the CEMR group: 69% (59%–77%) vs 50% (40%–60%) ($P = .011$) (Table 2). The en bloc resection rate in the UEMR group was also significantly higher than that in the CEMR group: 89% (81%–94%) vs 75% (65%–83%) ($P = .007$). Per-protocol analysis supported the results of the ITT analysis for the primary endpoint: R0 resection rates of 69% (59%–78%) vs 51% (41%–61%) ($P = .010$) in the UEMR and CEMR groups, respectively. There was no significant difference in the median (interquartile range) procedure times: 165 seconds (117–274 seconds) vs 175 seconds (130–266 seconds) ($P = .629$).

Table 2. Procedure-related Outcomes in this Study

Parameter	CEMR group (n = 102)	UEMR group (n = 108)	*P*
R0 resection	51	74	.011
Rate, % (95% CI)	50 (40–60)	69 (59–77)	
R1 resection	24	16	
RX resection	27	18	
En bloc resection	76	96	.007
Rate, % (95% CI)	75 (65–83)	89 (81–94)	
Piecemeal resection	26	12	
Median procedure time, *seconds* (IQR)	175 (130–266)	165 (117–274)	.629
Histological type, n (%)			.089
Sessile serrated adenoma/polyps	17 (17)	17 (16)	
Adenoma	67 (66)	70 (65)	
Intramucosal adenocarcinoma	15 (15)	15 (14)	
Submucosal adenocarcinoma			
<1000 μm	0	2 (1.9)	
≥1000 μm	2 (2.0)	1 (0.9)	
Others	1 (1.0)	3 (2.8)	

CI, confidence interval; IQR, interquartile range.

Table 3. Adverse Events in This Study

Adverse events	CEMR group (n = 102)	UEMR group (n = 108)
Delayed bleeding	2 (Grade 2[a])	3 (Grade 2[a])
≤48 h after procedure	2	3
>48 h after procedure	0	0
Intraprocedural perforation	0	0
Delayed perforation	0	0
Hyponatremia	0	0

[a]Based on the Common Toxicity Criteria for Adverse Events 4.03.

Adverse Events

There was no intraprocedural hemorrhage that required transfusion, interventional radiology, or surgery. Delayed bleeding from the treatment site, which was managed by endoscopic hemostasis, occurred in 2 patients in the CEMR group and 3 in the UEMR group within 48 hours after the procedure. Among those who developed delayed bleeding, 3 patients had undergone clip closure of the resection wound, and 2 had not. There was no intraprocedural perforation during the UEMR or CEMR procedure. The incidence of each adverse event did not differ significantly between the groups (Table 3).

Ancillary Analysis

Subset analysis suggested that UEMR was better for lesions ≥15 mm (P = .016) (Figure 3). Overall, however, UEMR showed a better trend for an R0 resection rate than CEMR did, irrespective of location, morphology, lesion size, or individual endoscopists' experience. The institutions with the lowest numbers of study subjects were enrolled (19 in C, 12 in D, and 5 in E), and there was no difference in R0 resection rate between UEMR and CEMR.

Discussion

To the best of our knowledge, this was the first multicenter, randomized controlled trial to prove that UEMR yielded significantly higher R0 resection and en bloc resection rates than CEMR for intermediate-size (10–20 mm) sessile colorectal lesions, without increasing the incidence of adverse events.

Various studies have reported an increased risk of piecemeal resection and local recurrence during endoscopic resection of polyps as the lesion size increases.[33–35] The ESD technique[9,10] was developed to remove large colorectal polyps en bloc. ESD reportedly yields an en bloc resection rate of 91.0% and an R0 resection rate of 82.9% for lesions with a mean size of 33 mm.[36] Moreover, ESD showed a low recurrence rate (2.0%) at 12 months postoperatively, which is substantially lower than the post-EMR recurrence rate of 13.8% reported by a recent meta-analysis.[37] Therefore, ESD is recommended for resection of large colorectal polyps, particularly those >20 mm in diameter.[8,38] In contrast, cold snare polypectomy is becoming a popular method for removal of small (≤9 mm) sessile colorectal polyps because it provides similar resection efficacy, with a low incidence of delayed bleeding.[8,39–41] However, cold snare polypectomy usually cannot resect polyps ≥10 mm in diameter because it does not use electrocautery. Accordingly, we chose intermediate-size (10–20 mm) sessile colorectal polyps for the present study. Although the European Society of Gastrointestinal Endoscopy Clinical Guidelines suggest hot-snare polypectomy with submucosal injection for removing sessile polyps 10–19 mm in size,[42] we found that UEMR was more effective than CEMR, in terms of better R0 and en bloc resection rates. Hence, we think that UEMR will become an alternative to CEMR. It could fill the gap for removing polyps ≤9 mm (indication for removal by cold snare polypectomy) and >20 mm (indication for ESD removal).

Although piecemeal resection is a well-known risk factor for local recurrence after EMR,[33–35] we used the R0 resection rate as a primary endpoint in this study. The R0 resection rate was 20% lower than the en bloc resection rate; a discrepancy mainly caused by rate of en bloc resection with histologically positive/indeterminate resection margins. One reason we evaluated R0 resection rate as a primary endpoint was to increase the objectivity of the outcome assessment. All pathologists involved in this study were blinded to the group allocation during histological examination. R0 resection was an objective parameter judged by pathologists who were blinded to the resection method, whereas en bloc resection was subjectively assessed by a nonblinded endoscopist. Oka et al[35] indicated in a multivariate analysis that only piecemeal resection was an independent significant factor for local recurrence after EMR, although univariate analysis showed significance for

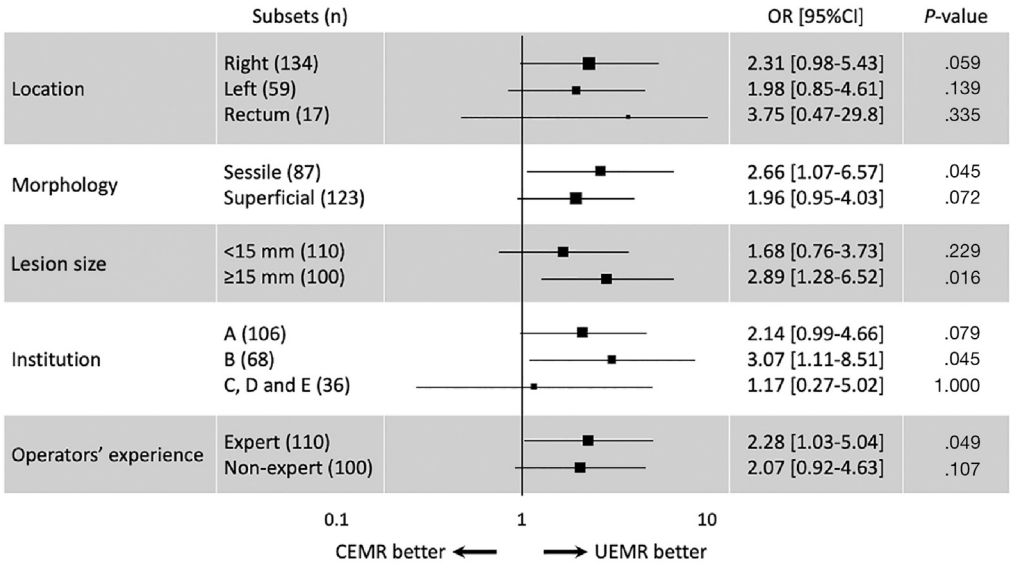


Figure 3. Subset analysis for R0 resection. CI, confidence interval; OR, odds ratio.

both piecemeal resection and a histologically positive resection margin. Therefore, the clinical importance of cauterizing an indeterminate margin during en bloc resection is uncertain. However, Klein et al[43] demonstrated that prophylactic thermal ablation of endoscopically clear resection margins after complete EMR significantly reduced incidence of local recurrence, suggesting that cauterized resection margins harbor viable neoplastic cells. Nevertheless, UEMR improved both the R0 and en bloc resection rates, so the clinical benefit of UEMR is well established.

UEMR was first described by Binmoeller et al[11] in 2012 for removing large, flat colorectal lesions. The concept of UEMR was developed from endoscopic ultrasound images of the digestive tract. Binmoeller et al[11] noticed that water immersion decreased the luminal extension force, increased mucosal and submucosal buoyancy, and made the mucosa, including the lesion, float upward into the lumen, while the muscularis propria remained circular behind the submucosa (Figure 4*A* and *B*). As a result, sessile or flat mucosal lesions become small and polypoid, which facilitates their snaring, thereby avoiding perforation. Moreover, water immersion minimizes luminal distension, flexure angulation, and loop formation, which yield better visualization and maneuverability of the endoscope.[44–46] Accordingly, the underwater resection technique facilitates removal of sessile colorectal lesions.[11] In contrast, submucosal injection often increases the surface area of the lesion, increases mucosal tension, decreases the difference in the level of the lesion from the surrounding mucosa, and makes snare capture more difficult[47,48] (Figure 4*C* and *D*).

UEMR requires maneuvers different from those used with CEMR. In practice, we think it is important to fill the entire lumen only with fluid, so we always deflate the lumen completely and then fill it with fluid. When there is remnant air in the lumen, we may have to move the patient's position to submerge the lesion. Moreover, the remnant air could create a pressure gradient and push the fluid away from the luminal compartment. When all the air is removed, however, the lumen collapses and is completely filled with fluid irrespective of the patient's position. The fluid remains in the lumen, and the lesion protrudes into the lumen regardless of gravity. Therefore, it is not necessary to change the patient's position during the UEMR procedure. Also, in cases with unclear endoscopic vision, endoscopists are familiar with air insufflation but, during UEMR, it is better to infuse the fluid to expand the lumen and maintain a good endoscopic view. Therefore, for the beginner, we recommend that the air insufflation button of the endoscopy machine be switched off. In the original method of UEMR, distilled water was used for immersion to avoid excessive electrical conduction; however, in case of a large volume of fluid infusion, water intoxication (hyponatremia) was reported.[49] We therefore used normal saline for water immersion in this study. Adverse events related to electrolyte abnormality or excessive diathermic mucosal injury were not observed, although further investigation is required to determine the appropriate fluid for UEMR.

In the subset analysis, the trend for a higher R0 resection rate with UEMR was not apparent in institutions where the level of experience was low (Institutions C–E), suggesting that the UEMR operators require to gain more experience. In institutions with a high volume of experience with UEMR (Institutions A and B), although we invited general endoscopists to participate who were not directly involved in this study, there was a better R0 resection rate with UEMR than with CEMR. Moreover, although approximately half of the UEMR procedures in this study were performed by nonexpert endoscopists, UEMR tended to have a better R0 resection rate, irrespective of endoscopists' individual experience. Therefore, UEMR is likely to become a widely accepted method in daily clinical practice.

In this study, various types of snare were used according to their availability in the participating hospitals. Originally, Binmoeller et al[11] used a duckbill snare, but we performed UEMR with various snares. In general, thin, soft snares are preferred for capturing the mucosa efficiently. A snare of the

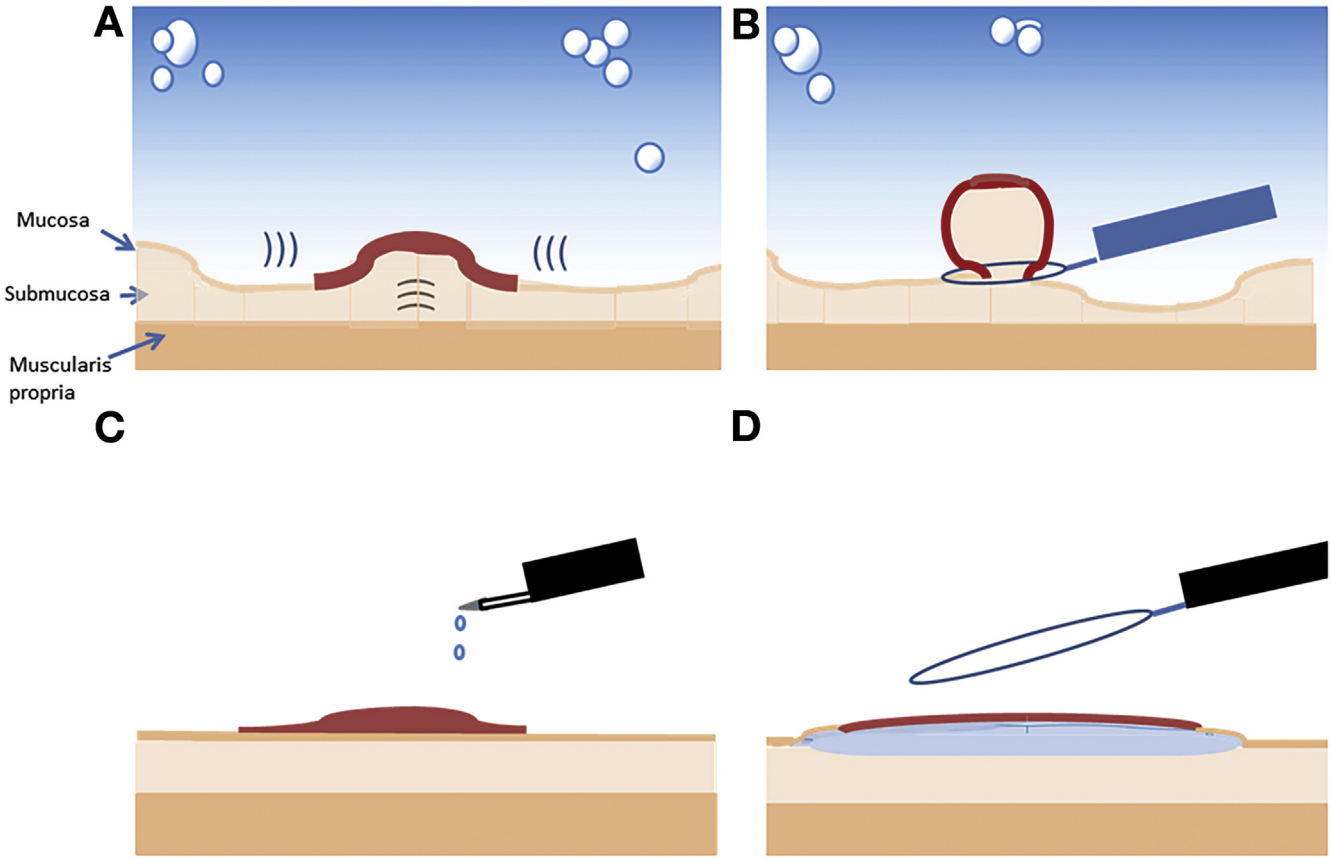


Figure 4. Principal difference between underwater and conventional injection EMR for sessile colorectal lesions. (*A*) Air deflation and water immersion lift and float a sessile lesion away from the muscularis propria. (*B*) The mucosa, including a sessile lesion, is easily captured as a pseudopedicle. (*C* and *D*) During conventional EMR, submucosal injection often makes a sessile lesion flattened and enlarged, and lesion snaring is difficult.

same or larger size than the lesion was chosen for UEMR. Even with a snare with the same size as the lesion, it was possible to capture the lesion completely, as it became smaller underwater.

Non–granular-type, laterally spreading tumors (LST-NGs) often have fibrotic areas in the submucosa,[50] causing unsatisfactory lifting by submucosal injection and making CEMR difficult. Although this type of lesion was included in the present study, UEMR increased the chance of resection compared with CEMR. In a retrospective comparative study, Kim et al[51] showed that UEMR achieved a better complete endoscopic removal rate than CEMR for post-EMR recurrence. Thus, UEMR may be useful for intermediate-size lesions with fibrosis that are difficult to remove by CEMR. A future prospective study is needed to validate this result. In our study, there was no lesion that was difficult to remove with UEMR and easy to remove with CEMR. Because colonic ESD for LST-NGs is challenging, if UEMR works as well for LST-NGs >20 mm, it warrants further investigation.

We achieved a natural magnification effect for endoscopic images underwater, which facilitated examining the area at the edge of the resection wound for any residual lesion. Although an RGB sequential imaging system was used in this study, light artifacts were never increased underwater. In addition, when we found a residual lesion, UEMR allowed easy resection of small remnants because submucosal injection was not required for UEMR, and the surrounding mucosa after UEMR was softer than that after CEMR. Furthermore, closure of mucosal defects with an endoclip was easy in the UEMR group because, without mucosal injection of fluid, the edge of the surrounding mucosa was loose and soft. We consider these features additional advantages of UEMR.

In this study, we used endoscopic lesion size for analysis, so the histological lesion size may not have been accurately reflected. Most studies have indicated that endoscopic measurements usually overestimate the size of colonic polyps by as much as 20%; especially when the lesion size is >1 cm.[52–54] To improve diagnostic accuracy and interobserver variability,[55,56] we used biopsy forceps as a scale. Moreover, we used an opened snare with size of 10 to 26 mm to measure the lesion because we targeted 10- to 20-mm colonic polyps. To determine the surveillance interval, the histological polyp size may be more appropriate than the endoscopic size. However, to determine the resection method for removing a colonic polyp, we must use the endoscopic size because accurate measurement of histological size is impossible before resection. In addition, comparability of the primary outcome between the UEMR and CEMR groups was not affected by the measurement

method because both groups used the same endoscopic method to determine the lesion size. Accordingly, we believe that the use of the endoscopic lesion size in this study was clinically relevant.

This study had several limitations. First, although we achieved better R0 resection rates in the UEMR group, the recurrence rate was not evaluated. Only 105 patients (50.2%) underwent follow-up colonoscopy 1 year after the procedure. Doctors who order colonoscopic examinations are not always directly involved in the study, so when complete endoscopic removal is achieved, surveillance colonoscopy for 2 to 3 years is recommended in accordance with the Japanese guidelines.[57] Moreover, because we did not require scar biopsy, post-EMR scarring was not identified in all patients who were followed. Thus, a future well-designed, highly compliant longitudinal study is needed to clarify the difference in local recurrence after UEMR and CEMR. Second, the operating endoscopists were not blinded to the group allocation. This limitation was the most important, although unmanageable problem for a randomized control trial using endoscopy. In this regard, we invited general endoscopists who were not coauthors in this study to be some of the operators. We believe that endoscopists always attempt to achieve en bloc/R0 resection for small-to-intermediate lesions in clinical practice regardless of the resection method, and this reduced any bias caused by the nonblinded procedure. In fact, R0 resection rate of CEMR in this study was consistent with that in a previous report.[58] Third, patients with pedunculated lesions were excluded from the study. For pedunculated polyps, UEMR may increase the R0 resection rate, but en bloc resection is also possible with CEMR with or without submucosal fluid injection. Therefore, we excluded patients with pedunculated polyps to highlight the benefits of UEMR.

In conclusion, our randomized study suggests that UEMR significantly increases the R0 and en bloc resection rates without increasing the incidence of adverse events and procedure time. On the basis of this evidence, the use of UEMR should be encouraged.

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.2019.04.005.

References

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015. JAMA Oncol 2017;3:524.
2. World Cancer Research Fund International. Colorectal cancer statistics. Available at: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/colorectal-cancer-statistics/. Accessed June 22, 2019.
3. International Agency for Research on Cancer. CANCER TODAY, CANCER FACT SHEETS, COLORECTAL CANCER. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf. Accessed on June 22, 2019.
4. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
5. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687–696.
6. Hurlstone DP, Sanders DS, Cross SS, et al. Colonoscopic resection of lateral spreading tumours: a prospective analysis of endoscopic mucosal resection. Gut 2004;53:1334–1339.
7. Hotta K, Fujii T, Saito Y, et al. Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 2009;24:225–230.
8. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017;49:270–297.
9. Yamamoto H, Sunada K, Miyata T, et al. Endoscopic submucosal dissection using sodium hyaluronate for large superficial tumors in the colon. Dig Endosc 2004;16:178–181.
10. Yahagi N, Fujishiro M, Imagawa A, et al. Endoscopic submucosal dissection for the reliable en bloc resection of colorectal mucosal tumors. Dig Endosc 2004;16(Suppl):S89–S92.
11. Binmoeller KF, Weilert F, Shah J, et al. "Underwater" EMR without submucosal injection for large sessile colorectal polyps (with video). Gastrointest Endosc 2012;75:1086–1091.
12. Siau K, Ishaq S, Cadoni S, et al. Feasibility and outcomes of underwater endoscopic mucosal resection for ≥10 mm colorectal polyps. Surg Endosc 2018;32:2656–2663.
13. Wang AY, Flynn MM, Patrie JT, et al. Underwater endoscopic mucosal resection of colorectal neoplasia is easily learned, efficacious, and safe. Surg Endosc 2014;28:1348–1354.
14. Uedo N, Nemeth A, Johansson G, et al. Underwater endoscopic mucosal resection of large colorectal lesions. Endoscopy 2014;47:172–174.
15. Kawamura T, Sakai H, Ogawa T, et al. Feasibility of underwater endoscopic mucosal resection for colorectal lesions: a single center study in Japan. Gastroenterol Res 2018;11:274–279.
16. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726–732.
17. Rex DK, Ponugoti P, Kahi C. The "valley sign" in small and diminutive adenomas: prevalence, interobserver agreement, and validation as an adenoma marker. Gastrointest Endosc 2017;85:614–621.
18. Tadepalli US, Feihel D, Miller KM, et al. A morphologic analysis of sessile serrated polyps observed during

routine colonoscopy (with video). Gastrointest Endosc 2011;74:1360–1368.
19. Yamashina T, Takeuchi Y, Uedo N, et al. Diagnostic features of sessile serrated adenoma/polyps on magnifying narrow band imaging: a prospective study of diagnostic accuracy. J Gastroenterol Hepatol 2015;30:117–123.
20. Hayashi N, Tanaka S, Hewett DG, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification. Gastrointest Endosc 2013;78:625–632.
21. Kimura T, Yamamoto E, Yamano H-O, et al. A novel pit pattern identifies the precursor of colorectal cancer derived from sessile serrated adenoma. Am J Gastroenterol 2012;107:460–469.
22. Kudo Se, Lambert R, Allen JI, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc 2008;68:S3–S47.
23. Tanaka S, Hayashi N, Oka S, et al. Endoscopic assessment of colorectal cancer with superficial or deep submucosal invasion using magnifying colonoscopy. Clin Endosc 2013;46:138–146.
24. Matsuda T, Fujii T, Saito Y, et al. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 2008; 103:2700–2706.
25. Fujimoto K, Fujishiro M, Kato M, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. Dig Endosc 2014;26:1–14.
26. Kato M, Uedo N, Hokimoto S, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment: 2017 appendix on anticoagulants including direct oral anticoagulants. Dig Endosc 2018;30:433–440.
27. Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma. 2nd English Edition. Tokyo: Kanehara & Co., Ltd., 2009.
28. Taves D. Minimization: a new method of assigning patients to treatment and control groups. Clin Pharmacol Ther 1974;15:443–453.
29. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.03. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. Accessed June 22, 2019.
30. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446–454.
31. Lee EJ, Lee JB, Lee SH, et al. Endoscopic treatment of large colorectal tumors: comparison of endoscopic mucosal resectin, endoscopic mucosal resection-precutting, and endoscopic submucosal dissection. Surg Endosc 2012;26:2220–2230.
32. Sato T, Fukuzawa M, Gotoda T, et al. Comparison of clinical outcomes between colorectal EMR and ESD. J Tokyo Med Univ 2016;74:154–162.
33. Knabe M, Pohl J, Gerges C, et al. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. Am J Gastroenterol 2014;109:183–189.
34. Mannath J, Subramanian V, Singh R, et al. Polyp recurrence after endoscopic mucosal resection of sessile and flat colonic adenomas. Dig Dis Sci 2011;56:2389–2395.
35. Oka S, Tanaka S, Saito Y, et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol 2015;110:697–707.
36. Fuccio L, Hassan C, Ponchon T, et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. Gastrointest Endosc 2017;86:74–86.
37. Hassan C, Repici A, Sharma P, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut 2016;65:806–820.
38. Watanabe T, Muro K, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 2018;23:1–34.
39. Kawamura T, Takeuchi Y, Asai S, et al. A comparison of the resection rate for cold and hot snare polypectomy for 4–9 mm colorectal polyps: a multicentre randomised controlled trial (CRESCENT study). Gut 2018;67:1950–1957.
40. Matsuura N, Takeuchi Y, Yamashina T, et al. Incomplete resection rate of cold snare polypectomy: a prospective single-arm observational study. Endoscopy 2017; 49:251–257.
41. Yamashina T, Fukuhara M, Maruo T, et al. Cold snare polypectomy reduced delayed postpolypectomy bleeding compared with conventional hot polypectomy: a propensity score-matching analysis. Endosc Int Open 2017;5:E587–E594.
42. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017;49:270–297.
43. Klein A, Tate DJ, Jayasekeran V, et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. Gastroenterology 2019;156:604–613.e3.
44. Leung JW, Thai A, Yen A, et al. Magnetic endoscope imaging (ScopeGuide) elucidates the mechanism of action of the pain-alleviating impact of water exchange colonoscopy: attenuation of loop formation. J Interv Gastroenterol 2012;2:142–146.
45. Leung FW, Leung JW, Mann SK, et al. The water method significantly enhances patient-centered outcomes in sedated and unsedated colonoscopy. Endoscopy 2011; 43:816–821.
46. Sakamoto T, Abe S, Yoshida MK, et al. Endocuff-assisted underwater snare polypectomy in complex ascending colon neoplasia. Endoscopy 2018;50:E136–E137.
47. Nelson DB. Techniques for difficult polypectomy. Med Gen Med 2004;6:12.
48. Binmoeller KF. Underwater endoscopic mucosal resection. J Interv Gastroenterol 2014;4:113–116.
49. Binmoeller KF, Shah JN, Bhat YM, Kane SD. "Underwater" EMR of sporadic laterally spreading nonampullary duodenal adenomas (with video). Gastrointest Endosc 2013;78:496–502.

50. Nagai K, Hayashi Y, Honma K, et al. Adenoma of colorectal laterally spreading tumor nongranular type with biological phenotypic features similar to cancer. J Gastroenterol Hepatol 2018;33:1853–1863.
51. Kim HG, Thosani N, Banerjee S, et al. Underwater endoscopic mucosal resection for recurrences after previous piecemeal resection of colorectal polyps (with video). Gastrointest Endosc 2014;80:1094–1102.
52. Anderson BW, Smyrk TC, Anderson KS, et al. Endoscopic overestimation of colorectal polyp size. Gastrointest Endosc 2016;83:201–208.
53. Morales TG, Sampliner RE, Garewal HS, et al. The difference in colon polyp size before and after removal. Gastrointest Endosc 1996;43:25–28.
54. Atalaia-Martins C, Marcos P, Leal C, et al. Variation between pathological measurement and endoscopically estimated size of colonic polyps. Portuguese J Gastroenterol 2019;26:163–168.
55. Kim JH, Park SJ, Lee JH, et al. Is forceps more useful than visualization for measurement of colon polyp size? World J Gastroenterol 2016;22:3220–3226.
56. Sakata S, McIvor F, Klein K, et al. Measurement of polyp size at colonoscopy: a proof-of-concept simulation study to address technology bias. Gut 2018;67:206–208.
57. Tanaka S, Saitoh Y, Matsuda T, et al. Evidence-based clinical practice guidelines for management of colorectal polyps. J Gastroenterol 2015;50:252–260.
58. Yoshida N, Naito Y, Inada Y, et al. Endoscopic mucosal resection with 0.13% hyaluronic acid solution for colorectal polyps less than 20 mm: a randomized controlled trial. J Gastroenterol Hepatol 2012;27:1377–1383.

Received October 23, 2018. Accepted April 1, 2019.

Reprint requests
Address requests for reprints to: Noriya Uedo, Department of Gastrointestinal Oncology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka 541-8567, Japan. e-mail: noriya.uedo@gmail.com; fax: +81-6-6945-1902.

Acknowledgments
The authors express gratitude to Professors Ian Grimm, Sauid Ishaq, and Sergio Cadoni for providing meaningful comments and to all endoscopists and health care practitioners who supported this study. We thank Cathel Kerr, BSc, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Author contributions: Study concept and design: Takeshi Yamashina and Noriya Uedo; Acquisition of data: Takeshi Yamashina, Tomofumi Akasaka, Taro Iwatubo, Takuji Akamatsu, Takuji Kawamura, and Toshihiro Kusaka; Analysis and interpretation of data: Takeshi Yamashina, Noriya Uedo, and Toshio Shimokawa; Drafting of the manuscript: Takeshi Yamashina and Noriya Uedo; Critical revision of manuscript: Takeshi Yamashina, Noriya Uedo, Tomofumi Akasaka, Taro Iwatubo, Yasuki Nakatani, Takuji Akamatsu, Takuji Kawamura, Yoji Takeuchi, Shigehiko Fujii, and Toshihiro Kusaka; Administrative support: Takeshi Yamashina, Tomofumi Akasaka, and Taro Iwatubo; Guarantor of the article: Takeshi Yamashina and Noriya Uedo.

Conflicts of interest
The authors disclose no conflicts.

Supplementary Table 1. Operators' Experiences

Number of endoscopists	28
Approximate numbers of colonoscopy experienced	
<1000	4
1000 to <3000	16
3000 to <6000	5
≥6000	3
Approximate numbers of colonic EMR experienced	
<100	0
100 to <300	7
300 to <600	10
≥600	11
Approximate numbers of colonic ESD experienced	
<10	11
10 to <30	5
30 to <60	4
≥60	8
Approximate numbers of esophagogastroduodenoscopy experienced	
<1000	0
1000 to <3000	7
3000 to <6000	14
≥6000	7
Certification from Japanese Gastroenterological Endoscopy Society	
Yes	17
No	11

Supplementary Table 2. Type of Videocolonoscope Used in This Study

	CEMR group	UEMR group
CF-HQ290L/I[a]	47	52
CF-HQ290ZL/I[a]	11	16
CF-H260AZI[a]	9	0
CF-Q260DI[a]	2	0
PCF-H290ZI[a]	6	8
PCF-H290L/I[a]	1	1
PCF-Q260AZI[a]	16	24
PCF-Q260AI[a]	5	6
EC-L600ZP7[b]	2	0
EC-L600MP7[b]	1	0
Unknown	2	1

[a]Olympus Medical Systems, Tokyo, Japan.
[b]Fujifilm, Tokyo, Japan.

Supplementary Table 3. Type of Cap Used in This Study

	CEMR group	UEMR group
Disposable distal attachments[a] (D-201)	56	59
Distal hood[a] (15002, MAJ-1991)	33	35
Elastic Touch Slit and Hole[b] (16675)	9	10
OBLICLEAR[b] (16651)	1	2

[a]Olympus Medical Systems, Tokyo, Japan.
[b]Top Corporation, Tokyo, Japan.

Supplementary Table 4. Types of Electrosurgical Unit and Settings

Institution	Electrosurgical unit		
	Intelligent Cut and Coagulation 200[a]	VIO 300D[a]	ESG-100[b]
A		• Endo-cut Q mode, Effect 3, Duration 2, and Interval 4 • Forced coagulation mode, 40 W	
B	• Endo-cut off, Effect 3, 30W • Forced coagulation mode, 15 W	• Auto cut mode, Effect 3, 30 W • Forced coagulation mode, Effect 1, 15 W	
C	• Endo-cut on, Effect 3, 120 W • Forced coagulation, 30 W	• Endo-cut Q mode, Effect 2, Duration 2, and Interval 3	
D			• Pulse-cut slow mode, 20 W • Forced coagulation 2 mode, 15 W
E			• Forced coagulation 1, 10 W

[a]ERBE Elektromedizin, Tübingen, Germany.
[b]Olympus Medical Systems, Co. Ltd, Tokyo, Japan.

Supplementary Table 5. Types of Snare Used in This Study

	CEMR group	UEMR group
Captivator II 10 mm[a] (M00561221)	10	14
Captivator II 15 mm[a] (M00561231)	35	39
Rotatable snare 13 mm[a] (M00561821)	6	4
Profile 13 mm[a] (M00562531)	0	1
DRAGONARE 26 mm[b] (BSDA-217)	35	38
Snare Master 20 mm[c] (SD-210U-15)	3	2
Snare Master 25 mm[c] (SD-210U-25)	9	6
Snare Master Plus 15 mm[c] (SD-400U-15)	0	1
Histolock 14 mm[d] (00711117 or 00711871)	2	0
Unknown	2	3

[a]Boston Scientific, Marlborough, MA.
[b]Xemex, Tokyo, Japan.
[c]Olympus Medical Systems, Tokyo, Japan.
[d]US Endoscopy, Mentor OH.

Supplementary Table 6. Antithrombotic Agents Taken by Subjects in This Study

	CEMR group	UEMR group
Continued antithrombotic therapy		
Aspirin	2	3
Cilostazol	0	0
Dabigatran	0	1
Warfarin	0	1
Limaprost alfadex	1	1
Aspirin + cilostazol[a]	1	0
Discontinued antithrombotic therapy		
Rivaroxaban	2	2
Apixaban	1	0
Edoxaban	1	0
Dabigatran + cilostazol (with heparin bridging)[b]	1	0
Warfarin	0	1
Warfarin (with heparin bridging)	0	1
Warfarin + aspirin + cilostazol (with heparin bridging)[c]	0	1
Aspirin	2	2
Limaprost alfadex	2	0
Cilostazol	1	0
Clopidogrel	1	1
Clopidogrel + aspirin	1	0

[a]Discontinued only cilostazol.
[b]Discontinued dabigatran and cilostazol.
[c]Discontinued warfarin and aspirin.