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Underwater versus conventional endoscopic mucosal resection for colorectal lesions: a systematic review and meta-analysis

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ABSTRACT

Background and study aims Underwater endoscopic mucosal resection (UEMR) for colorectal polyps has been reported to have good outcomes in recent studies. We conducted a systematic review and meta-analysis comparing the effectiveness and safety of UEMR to conventional EMR (CEMR).

Methods A comprehensive search of multiple databases (through May 2020) was performed to identify studies that reported outcome of UEMR and CEMR for colorectal lesions. Outcomes assessed included incomplete resection, rate of recurrence, en bloc resection, adverse events (AEs) for UEMR and CEMR.

Results A total of 1,651 patients with 1,704 polyps were included from nine studies. There was a significantly lower rate of incomplete resection (odds ratio [OR]: 0.19 (95% confidence interval (CI), 0.05–0.78, $P=0.02$) and polyp recurrence (OR: 0.41, 95% CI, 0.24–0.72, $P=0.002$) after UEMR. Compared to CEMR, rates overall complications (relative risk [RR]: 0.66 (95% CI, 0.48–0.90) ($P=0.008$), and intra-procedural bleeding (RR: 0.59, 95% CI, 0.41–0.84, $P=0.004$) were significantly lower with UEMR. The recurrence rate was also lower for large non-pedunculated polyps ≥ 10 mm (OR 0.24, 95% CI, 0.10–0.57, $P=0.001$) and ≥ 20 mm (OR 0.14, 95% CI, 0.02–0.72, $P=0.01$). The rates of en bloc resection, delayed bleeding, perforation and post-polypectomy syndrome were similar in both groups ($P>0.05$).

Conclusions In this systematic review and meta-analysis, we found that UEMR is more effective and safer than CEMR with lower rates of recurrence and AEs. UEMR use should be encouraged over CEMR.

Introduction

Endoscopic mucosal resection (EMR) is the primary treatment modality for large and/or sessile colorectal polyps [1, 2]. In the conventional EMR (CEMR) technique, a submucosal fluid injection creates a cushion to separate the deeper muscularis mucosa from the superficial epithelial layer that contains the lesion. The submucosal injection is performed to prevent full thickness perforation and deep thermal injury by increasing the distance between the electrocautery current and the transmural space [3]. Submucosal injection assisted EMR has been widely accepted technique for colorectal lesions and has largely replaced surgical resection. The European society of gastrointestinal endoscopy (ESGE) recommends EMR with submucosal injection for sessile or flat polyps ≥ 10 mm in size [3]. The alternative approaches, including surgery and endoscopic submucosal dissection (ESD), are costly, more time consuming, require more resources, and ESD is not readily available in the US [4, 5]. In spite of these advantages, CEMR for large polyps have been associated with high rates of incomplete resection and local recurrence of 15 % to 30 % on follow up [2, 5–7].

In underwater EMR (UEMR), the mucosa and submucosa float away from muscularis propria, facilitating polyectomy [8]. Removal of intraluminal air also decreases colonic wall tension, which permits the colon wall to assume its natural collapsed state. It was first described by Binmoeller and colleagues in 2012 based on observation during endosonography [8]. Multiple studies have reported good results of UEMR along with low rate of adverse events [9–13], but data-comparing UEMR to CEMR has not been systematically reviewed. We performed a systematic review and meta-analysis comparing the safety and effectiveness of UEMR and CEMR for the resection of colorectal polyps.

Methods

Search strategy

We conducted a comprehensive search of several databases from inception to May 2020. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process and other non-indexed citations, Ovid Embase, Ovid Cochrane Central Register of Controlled trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. An experienced medical librarian using inputs from the study authors helped with the literature search. Controlled vocabulary supplemented with keywords was used to search for studies of interest. The full search strategy is available in **Appendix 1**. The MOOSE and PRISMA checklist were followed and are provided in **Appendix 2** and **Appendix 3** [14, 15].

Study selection

All studies that reported clinical outcomes of CEMR and UEMR were included, irrespective of sample-size, inpatient/ outpatient setting, and geography, as long as they provided any data needed for the analysis.

Studies done in pediatric population (Age < 18 years), and studies not published in English language were excluded. In cases of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form and quality score independently by two authors (RG and BPM). Primary study authors were contacted via email for additional data or any clarification on data.

The Newcastle-Ottawa scale for cohort studies and Jadad score for randomized control trials was used to assess the quality of studies [16]. This Newcastle Ottawa quality score consists of eight questions and Jadad score consists of five questions, the details of which are provided in **Supplementary Table 1**.

Outcomes assessed

The primary outcome was rate of any incomplete resection. Incomplete resection was defined as presence of macroscopic residual polyp based on endoscopist assessment reported by study authors. Secondary outcomes included R0 resection, recurrence/residual polyp on follow up colonoscopy, adverse events and en bloc resection. The R0 resection was defined as margins clear of any abnormal tissue based on histologic assessment. The recurrence/residual rate was based on first follow up colonoscopy and presence of abnormal lesion at the site of previous intervention. The recurrence/residual polyp was described on endoscopic and histologic assessment by study authors. The adverse events were further classified into intra-procedural or delayed bleeding, perforation and post-polypectomy syndrome (PPS). Intra-procedural bleeding was defined as immediate bleeding requiring endoscopic hemostasis and delayed bleeding was defined as post-procedural bleeding within 2 to 4 weeks of intervention. En bloc resection was defined as lesion resection as one piece rather than in multiple small pieces

Subgroup analysis was performed for non-pedunculated polyps ≥ 10 mm and ≥ 20 mm.

Statistical analysis

We used meta-analysis techniques to calculate the odds ratio for resection outcomes and relative risks for complications outcome using inverse variance equation and random-effects model as described by DerSimonian and Laird [17]. We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity,[18–20] and the I^2 statistics [21, 22]. In this, values of < 30 %, 30 % to 60 %, 61 % to 75 %, and > 75 % were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [23]. If heterogeneity was present, we attempted to assess the reasons of the heterogeneity. $P < 0.05$ was used to define statistical significance between the groups.

All analyses were performed using RevMan 5.0 (Cochrane collaboration) statistical software [24].

Results

Search results and population characteristics

From an initial 242 studies, 144 records were screened and 41 full-length articles were assessed. Nine studies were included in the final analysis that reported and compared outcomes of UEMR and CEMR [13, 25–32]. The schematic diagram of study selection is illustrated in **Supplementary Fig. 1**. In one study, we excluded some small polyps < 10 mm as they were resected with underwater cold snare rather than EMR and did not meet inclusion criteria [32].

A total of 1,651 patients with 1,704 polyps were included from 9 studies in the final analysis. Out of 1,704 polyps, 891 were resected by CEMR and 813 were resected by UEMR. The mean age ranged from 62.3 to 70 years and majority of the patients were males (66.4%, n = 1,132). The mean polyp size ranged from 9.9 mm to 30.2 mm in CEMR group and 9.9 mm to 27.5 mm in UEMR group. The type of polyp based on Paris classification was available in seven studies including 1,266 (88.7%) non-pedunculated polyps (647 CEMR and 619 UEMR). The mean duration of procedure ranged from 3.4 to 26.4 minutes in CEMR group and 1.5 to 13.3 minutes in UEMR group. The baseline characteristics and data on assessed outcomes are shown in ▶ **Table 1** and ▶ **Table 2**, respectively.

There were seven studies reporting outcomes on non-pedunculated polyps ≥ 10 mm. Amongst the total of 1,266 non-pedunculated polyps, 95.1% (n = 1,204, 612 CEMR and 592 UEMR) were ≥ 10 mm and 23.2% (n = 294, 166 CEMR and 128 UEMR) were ≥ 20 mm. Data on assessed outcomes for non-pedunculated polyps ≥ 10 mm and ≥ 20 mm are shown in **Supplementary Table 2** and **Supplementary Table 3** respectively.

Characteristics and quality of included studies

Five studies were retrospective [13, 25, 27, 29, 31] one prospective [28] and three were randomized controlled trials [26, 30, 32]. Six studies were full-text articles [13, 25, 28–30, 32] and three were published abstracts [26, 27, 31]. Amongst the six cohort studies, four were of high quality and two were medium quality. Based on Jadad score, two of three randomized trials were of good quality and one was of poor quality. The quality assessment is shown in **Supplementary Table 1**.

Meta-analysis outcomes

The rate of incomplete resection in UEMR group was significantly lower than CEMR group (odds ratio [OR]: 0.19, 95% confidence interval [CI], 0.05–0.78, $I^2 = 23$, $P = 0.02$) (▶ **Fig. 1a**). The rate of R0 resection was provided in two studies. From these studies, we noticed significantly higher odds of R0 resection in UEMR as compared to CEMR with OR of 2.20 (95% CI, 1.26–3.83, $I^2 = 0$, $P = 0.0005$) (▶ **Fig. 1b**). The recurrence rate and follow up was reported in six studies. A total of 338 and 210 patients underwent follow up in CEMR and UEMR group respectively. The follow-up duration ranged from 3 to 14 months after the index procedure. The recurrence rate was significantly lower in patients who underwent UEMR than in patients who underwent CEMR (OR: 0.41, 95% CI, 0.24–0.72, $I^2 = 0$, $P = 0.002$) (▶ **Fig. 1c**).

There were a total of 160 adverse events, 91 (10.2%) in CEMR group and 59 (7.2%) in UEMR group. The most common complication was intra-procedural bleeding (73.7%, n = 118, 70 in CEMR group and 38 in UEMR group) followed by delayed bleeding (21.2%, n = 34), three cases of perforation, and two cases of PPS syndrome. There was one report of transient bacteremia after UEMR [26] and three cases (2 in CEMR and 1 in UEMR group) of muscle layer injury without perforation [13]. The rate of overall complications was significantly lower with UEMR compared to CEMR with relative risk (RR) of 0.66 (95% CI, 0.48–0.90, $I^2 = 0$), $P = 0.008$ (▶ **Fig. 2a**). This was primarily derived from significantly less incidence of intra-procedural bleeding in UEMR with RR of 0.59 (95% CI, 0.41–0.84, $I^2 = 0$), $P = 0.004$ (▶ **Fig. 2b**). There were 16 (1.8%) cases of delayed bleeding, two cases of perforation and one case of PPS in CEMR group, compared to 18 (2.2%) cases of delayed bleeding, one case of perforation and one case of PPS in UEMR group. Overall, the incidence of delayed bleeding (RR: 1.58, 95% CI, 0.75–3.33, $I^2 = 1$, $P = 0.24$), perforation (RR: 0.89, 95% CI, 0.14–5.62, $I^2 = 0$, $P = 0.90$), and PPS (RR: 1.08, 95% CI, 0.11–10.27, $I^2 = 0$, $P = 0.94$) were low in our study population and did not differ significantly amongst both groups (▶ **Fig. 3a**, ▶ **Fig. 3b**, ▶ **Fig. 3c**).

There was a higher trend of en bloc resection in UEMR group as compared to CEMR (OR: 1.33, 95% CI, 0.72–2.44, $I^2 = 82\%$), but this difference did not reach statistical significance ($P = 0.36$). Due to presence of substantial heterogeneity, we further inspected data from only prospective studies. Compared to CEMR, the rates of en bloc resections in UEMR were ~2.5-fold higher (OR: 2.48 (95% CI, 1.57–3.93, $I^2 = 39$, $P < 0.001$) with less heterogeneity in prospective studies (**Supplementary Fig. 2**).

Subgroup analysis of non-pedunculated polyps ≥ 10 mm

There were seven studies that provided data on polyp characteristics. A total of 1,204 non-pedunculated polyps ≥ 10 mm were included in the analysis. Compared to CEMR, odds of incomplete resection (OR: 0.26, 95% CI, 0.03–2.54, $I^2 = 55$, $P = 0.11$) were not significant but recurrence rate (OR: 0.24, 95% CI, 0.10–0.57, $I^2 = 0$, $P = 0.001$) was significantly lower in patients who underwent UEMR. There were no significant differences in rates of overall adverse events, delayed bleeding, perforation and PPS in both groups, however, UEMR had significantly lower risk of intra-procedural bleeding (RR: 0.64, 95% CI, 0.44–0.94, $I^2 = 0$, $P = 0.02$). The UEMR has again higher trend of en bloc resection with OR of 1.44 (95% CI, 0.74–2.78, $I^2 = 84$, $P = 0.28$) as compared to CEMR. This effect was stronger on including only prospective studies (OR: 2.48, 95% CI, 1.57–3.93, $I^2 = 39$, $P < 0.001$). Two studies did not show any statistically significant difference for R0 resection in UEMR vs. CEMR groups (OR: 1.62, 95% CI, 0.86–3.04, $I^2 = 52$, $P = 0.15$). These results are summarized in ▶ **Table 3**.

Subgroup analysis of non-pedunculated polyps ≥ 20 mm

There were five studies that provided data on outcomes of non-pedunculated polyps of size ≥ 20 mm. Compared to CEMR, there was no significant difference in rate of incomplete resection (OR: 0.86, 95% CI, 0.08–8.79, $I^2 = 11\%$, $P = 0.29$) and en bloc resection (OR: 0.90, 95% CI, 0.38–2.17, $I^2 = 58\%$, $p = 0.82$) with UEMR. There was again significantly low rate of recurrence with OR of 0.14 (95% CI, 0.02–0.72, $I^2 = 11\%$, $P = 0.01$) after UEMR as compared to CEMR. There was no difference in rates of complication in both groups with overall complications (RR: 2.17, 95% CI, 0.77–6.17, $I^2 = 0$, $P = 0.15$), intra-procedural bleeding (RR: 0.85, 95% CI, 0.15–4.73, $I^2 = 74\%$, $P = 0.85$), delayed bleeding (RR: 1.77, 95% CI, 0.23–13.34, $I^2 = 0\%$, $p = 0.84$), perforation (RR: 0.89, 95% CI, 0.09–8.39, $I^2 = 0$, $P = 0.92$), and PPS (RR: 0.92 (95% CI, 0.13–6.41, $I^2 = 0$, $P = 0.93$). We were unable to compare rate of R0 resection due to only

Table 1 Study and population characteristics.

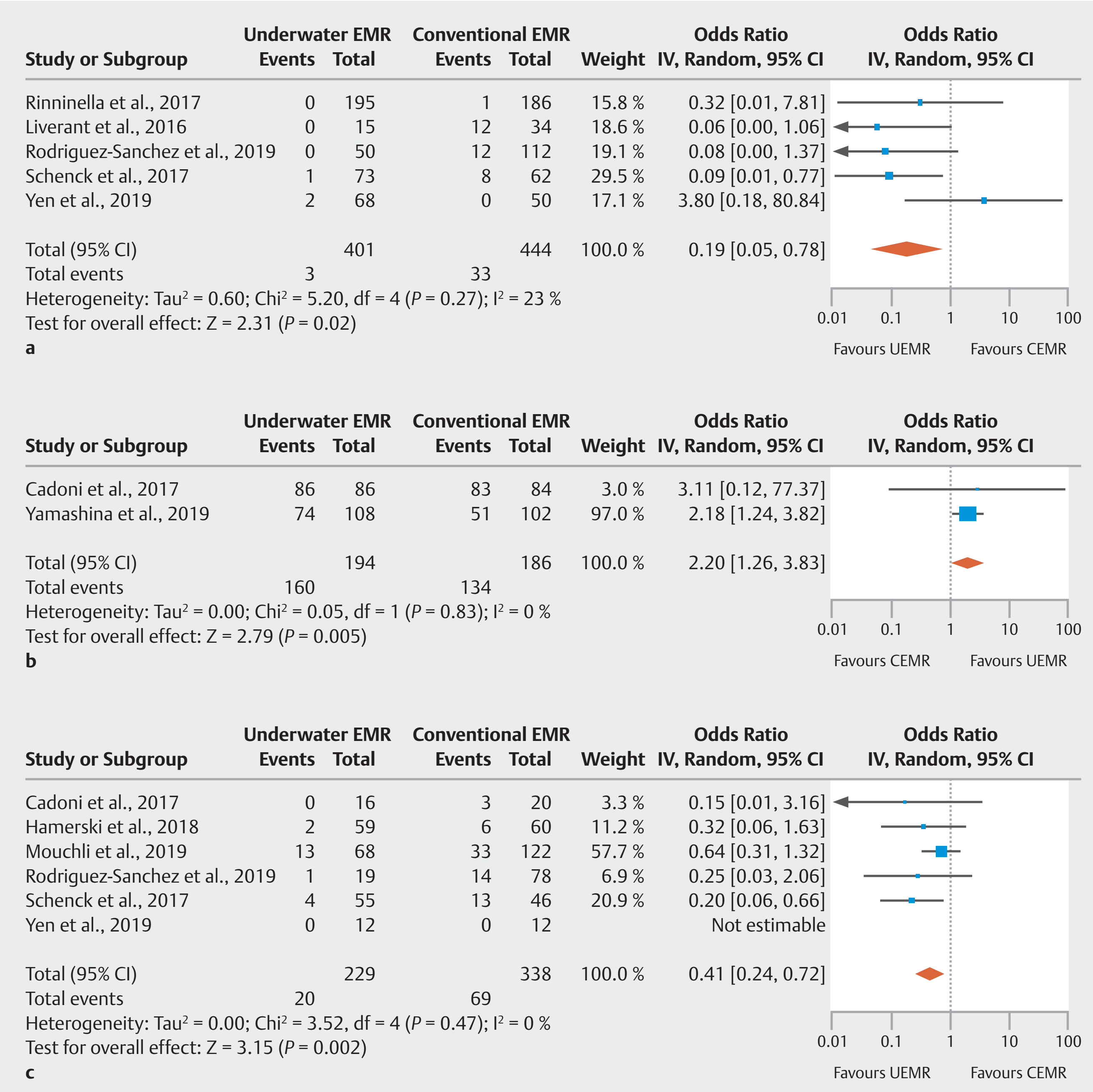
Author	Study type	Number of patients		Number of polyps		Age (median or mean ± SD)		Female (n)		Mean polyp size (mm, range, mean ± SD)		Nonpedunculated (n)		Right sided (%)		Duration (min, median or mean ± SD)	
		CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR
Liverant et al, 2016 [26]	Retrospective	39	32	48	39	63.4	63.8	22	14	17.2 (2–60)	27.5 (6–50)	NR	NR	46	64	NR	13.3
Cadoni et al, 2017 [24]	Retrospective	141	146	186	195	65.2	64.7	52	45	10.3	11.5	108	112	23.1	19.4	median 3.4	median 1.5
Chien et al, 2017 [13]	Retrospective	108	115	121	121	64.2 ± 10	64.1 ± 12.3	45	42	16.6 ± 6.5	17 ± 7.2	121	121	57.8	53.7	10.8 ± 8.3	8.6 ± 6.4
Schenck et al, 2017 [28]	Retrospective	53	46	62	73	62.3	62.8	18	19	21.9	25.4	57	72	82.3	67.1	NR	NR
Hamerski et al, 2018 [25]	RCT	179 total[1]	–	88	91	67.7 overall[1]	–	90 total[1]	–	28.1	29	NR	NR	81.5 total[2]	–	18.4	10.2
Rodriguez-Sanchez et al, 2019 [27]	Prospective	137 total[1]	–	112	50	66.25 ± 10.53 overall[1]	–	56 total[1]	–	30.38	20.78	112	50	52.6	76	26.14	9.82
Yamashina et al, 2019 [29]	RCT	102	108	102	108	68	70	27	44	13.5	14	102	108	66.6	61.1	median 2.91	median 2.75
Mouchli et al, 2019 [30]	Retrospective	122	68	122	68	64.4 ± 10	63.4 ± 12.5	59	32	NR	NR	NR	NR	NR	NR	NR	NR
Yen et al, 2019 [31]	RCT	127	128	50[1]	68	64.6 ± 8.3	64.4 ± 8.3	5	2	9.9 ± 5.8	9.9 ± 6.4	50	68	81.5	80.4	3.8 ± 0.34	5.4 ± 0.35

CEMR, convention endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection; RCT, randomized control trial; NR, not reported.
[1] We excluded small polyps < 10 mm as they were resected with cold snare rather than EMR.
[2] These values are reported for total number of patients in study as separate group values were not available.

▶ Table 2 Data on assessed outcome included in the analysis.

Author	En bloc resection		Incomplete resection		R0 resection		Adverse events		Intra-procedural bleeding		Delayed bleeding		Perforation		Post-polypectomy syndrome		Mean follow-up (months)	Recurrence per patient basis	
	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR	CEMR	UEMR		CEMR	UEMR
Liverant et al, 2016 [26]	13	8	12	0	NR	NR	2	2	0	0	1	2	0	0	1	0	NR	NR	NR
Cadoni et al, 2017 [24]	171	156	1	0	83	86	23	16	22	14	1	2	0	0	0	0	14	3/20	0/16
Chien et al, 2017 [13]	100	106	NR	NR	NR	NR	22	10	19	7	1	1	0	1	0	0	NR	NR	NR
Schenck et al, 2017 [28]	22	21	8	1	NR	NR	0	3	0	0	0	3	0	0	0	0	6.1	13/46	4/55
Hamerski et al, 2018 [25]	20	50	NR	NR	NR	NR	28	19	23	16	4	1	1	0	0	1	NR	6/60	2/59
Rodriguez-Sanchez et al, 2019 [27]	55	34	12	0	NR	NR	11	1	6	1	4	0	1	0	0	0	3–6	14/78	1/19
Yamashina et al, 2019 [29]	76	96	NR	NR	51	74	2	3	0	0	2	3	0	0	0	0	NR	NR	NR
Mouchli et al, 2019 [30]	NR	NR							2	0	3	6					5.8	33/122	13/68
Yen et al, 2019 [31]	32	48	0	2	NR	NR	3	5	3	5	0	0	0	0	0	0	3–6	0/12	0/12

CEMR, convention endoscopic mucosal resection; UEMR, underwater endoscopic mucosal resection; NR, not reported.



▶ **Fig. 1** Forest plot showing odds ratio of **a** incomplete resection, **b** R0 resection, and **c** recurrence comparing conventional and underwater endoscopic mucosal resection.

one study reporting this outcome for polyps > 20 mm. These results are also summarized in ▶ **Table 3**.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

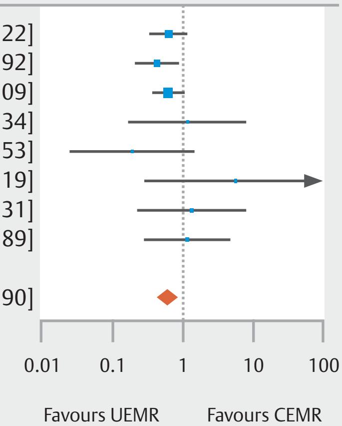
We assessed dispersion of the calculated rates using I^2 percentage values. The I^2 tell us what proportion of the dispersion is true vs. chance [20]. The I^2 is reported along with results in ▶ **Table 3**. Overall, there was low heterogeneity in our study outcomes

Publication bias

Publication bias was not assessed due to less than ten studies being included in the meta-analysis.

Study or Subgroup	Underwater EMR Events	Underwater EMR Total	Conventional EMR Events	Conventional EMR Total	Weight	Risk Ratio IV, Random, 95% CI
Cadoni et al., 2017	16	195	23	186	26.8 %	0.66 [0.36, 1.22]
Chien et al., 2017	10	121	22	121	19.9 %	0.45 [0.22, 0.92]
Hamerski et al., 2018	19	91	28	88	38.8 %	0.66 [0.40, 1.09]
Liverant et al., 2016	2	39	2	48	2.7 %	1.23 [0.18, 8.34]
Rodriguez-Sanchez et al., 2019	1	50	11	112	2.4 %	0.20 [0.03, 1.53]
Schenck et al., 2017	3	73	0	62	1.1 %	5.96 [0.31, 113.19]
Yamashina et al., 2019	3	108	2	102	3.1 %	1.42 [0.24, 8.31]
Yen et al., 2019	5	68	3	50	5.1 %	1.23 [0.31, 4.89]
Total (95% CI)		745		769	100.0 %	0.66 [0.48, 0.90]
Total events	59		91			

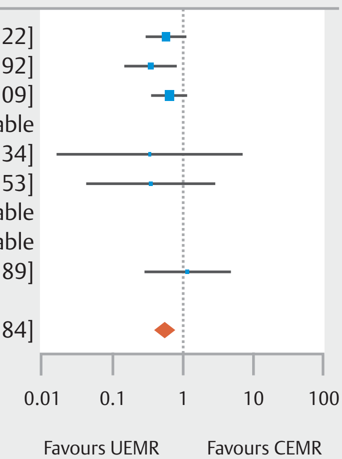
Heterogeneity: Tau² = 0.00; Chi² = 6.42, df = 7 (*P* = 0.49); I² = 0 %
Test for overall effect: Z = 2.63 (*P* = 0.008)



a

Study or Subgroup	Underwater EMR Events	Underwater EMR Total	Conventional EMR Events	Conventional EMR Total	Weight	Risk Ratio IV, Random, 95% CI
Cadoni et al., 2017	14	195	22	186	31.1 %	0.66 [0.36, 1.22]
Chien et al., 2017	7	121	19	121	18.5 %	0.45 [0.22, 0.92]
Hamerski et al., 2018	16	91	23	88	39.5 %	0.66 [0.40, 1.09]
Liverant et al., 2016	0	39	0	48		Not estimable
Mouchli et al., 2019	0	68	2	122	1.4 %	1.23 [0.18, 8.34]
Rodriguez-Sanchez et al., 2019	1	50	6	112	2.9 %	0.20 [0.03, 1.53]
Schenck et al., 2017	0	73	0	62		Not estimable
Yamashina et al., 2019	0	108	0	102		Not estimable
Yen et al., 2019	5	68	3	50	6.6 %	1.23 [0.31, 4.89]
Total (95% CI)		745		891	100.0 %	0.59 [0.41, 0.84]
Total events	43		75			

Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 5 (*P* = 0.73); I² = 0 %
Test for overall effect: Z = 2.89 (*P* = 0.004)



b

▶ **Fig. 2** Forest plot showing relative risk of **a** adverse events and **b** intra-procedural bleeding comparing conventional and underwater endoscopic mucosal resection.

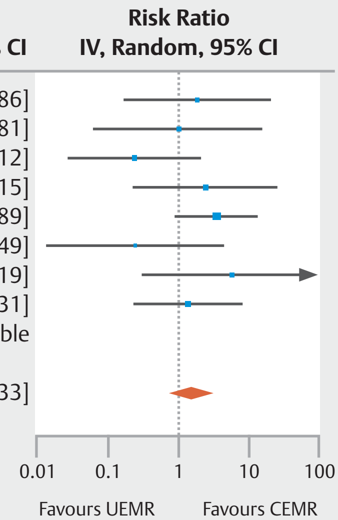
Discussion

Our analysis demonstrates that UEMR was significantly associated with less rates of incomplete resection (OR: 0.19, 95 % CI, 0.05–0.78, *P* = 0.02) and recurrence (OR: 0.41, 95 % CI, 0.24–0.72, *P* = 0.002) of colorectal polyps as compared to CEMR. In addition, UEMR was associated with almost half the risk of complications as compared to CEMR. This was mostly evident by significantly lesser odds of intra-procedural bleeding whereas odds of delayed bleeding, perforation and PPS were similar in both groups. UEMR has double the rate of R0 resection and is almost three times likely to lead to en bloc resection as compared to CEMR. UEMR advantages were also significantly demonstrated for non-pedunculated polyps ≥ 10 mm in terms of intra-procedural bleeding and recurrence rate. Even in non-pedunculated polyps ≥ 20 mm, recurrence rates were significantly lower in patients undergoing UEMR. Our study is the largest and first meta-analysis reporting and comparing outcomes of UEMR to CEMR.

Although UEMR has many advantages over CEMR, the major advantages are higher rates of complete resection and en bloc resection with significantly lower rates of recurrence. These effects were also evident in non-pedunculated polyps > 10 mm in size. UEMR was more effective in resection of larger lesion compared to CEMR. We speculate the advantage of complete resection likely translates into low rate of recurrence on follow up endoscopy. In addition, piecemeal resection has been reported to be an independent significant factor for local recurrence after CEMR [33]. This is extremely significant finding especially in real world setting where patient compliance and behavior plays a major role in follow up. Moreover, lower rates of recurrence will likely translate into lower cost and overall decreased burden on healthcare resources when applied to large population.

Study or Subgroup	Underwater EMR Events	Underwater EMR Total	Conventional EMR Events	Conventional EMR Total	Weight	Risk Ratio IV, Random, 95% CI
Cadoni et al., 2017	2	195	1	186	9.7 %	1.91 [0.17, 20.86]
Chien et al., 2017	1	121	1	121	7.3 %	1.00 [0.06, 15.81]
Hamerski et al., 2018	1	91	4	88	11.8 %	0.24 [0.03, 2.12]
Liverant et al., 2016	2	39	1	48	10.0 %	2.46 [0.23, 26.15]
Mouchli et al., 2019	6	68	3	122	30.4 %	3.59 [0.93, 13.89]
Rodriguez-Sanchez et al., 2019	0	50	4	112	6.6 %	0.25 [0.01, 4.49]
Schenck et al., 2017	3	73	0	62	6.4 %	5.96 [0.31, 113.19]
Yamashina et al., 2019	3	108	2	102	17.8 %	1.42 [0.24, 8.31]
Yen et al., 2019	0	68	0	50		Not estimable
Total (95% CI)		816		891	100.0 %	1.58 [0.75, 3.33]
Total events	18		16			

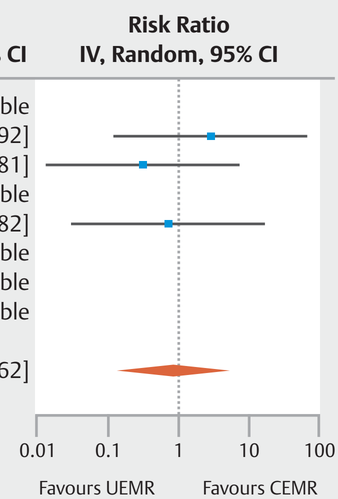
Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 7 (P = 0.44); I² = 0 %
Test for overall effect: Z = 1.20 (P = 0.23)



a

Study or Subgroup	Underwater EMR Events	Underwater EMR Total	Conventional EMR Events	Conventional EMR Total	Weight	Risk Ratio IV, Random, 95% CI
Cadoni et al., 2017	0	195	0	186		Not estimable
Chien et al., 2017	1	121	0	121	33.3 %	3.00 [0.12, 72.92]
Hamerski et al., 2018	0	91	1	88	33.3 %	0.32 [0.01, 7.81]
Liverant et al., 2016	0	39	0	48		Not estimable
Rodriguez-Sanchez et al., 2019	0	50	1	112	33.4 %	0.74 [0.03, 17.82]
Schenck et al., 2017	0	73	0	62		Not estimable
Yamashina et al., 2019	0	108	0	102		Not estimable
Yen et al., 2019	0	68	0	50		Not estimable
Total (95% CI)		745		769	100.0 %	0.89 [0.14, 5.62]
Total events	1		2			

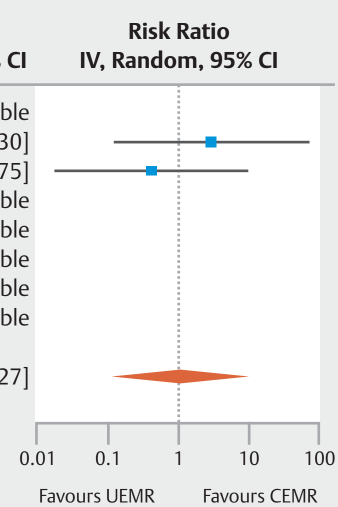
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0 %
Test for overall effect: Z = 0.12 (P = 0.90)



b

Study or Subgroup	Underwater EMR Events	Underwater EMR Total	Conventional EMR Events	Conventional EMR Total	Weight	Risk Ratio IV, Random, 95% CI
Cadoni et al., 2017	0	195	0	186		Not estimable
Chien et al., 2017	0	121	0	121	49.8 %	2.90 [0.12, 70.30]
Hamerski et al., 2018	1	91	0	88	50.2 %	0.41 [0.02, 9.75]
Liverant et al., 2016	0	39	1	48		Not estimable
Rodriguez-Sanchez et al., 2019	0	50	0	112		Not estimable
Schenck et al., 2017	0	73	0	62		Not estimable
Yamashina et al., 2019	0	108	0	102		Not estimable
Yen et al., 2019	0	68	0	50		Not estimable
Total (95% CI)		745		769	100.0 %	1.08 [0.11, 10.27]
Total events	1		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0 %
Test for overall effect: Z = 0.07 (P = 0.94)



c

► **Fig. 3** Forest plot showing relative risk of **a** delayed bleeding, **b** perforation, **c** and post-polypectomy syndrome comparing conventional and underwater endoscopic mucosal resection.

► **Table 3** Results of subgroup analysis of non-pedunclated polyps ≥ 10 mm and ≥ 20 mm comparing conventional endoscopic mucosal resection and underwater endoscopic mucosal resection.

	Nonpedunclated polyps ≥ 10 mm[1]	Nonpedunclated polyps ≥ 20 mm[1] (OR)
Incomplete resection (OR)	0.26 (0.03, 2.54), $P = 0.11$, $I^2 = 55\%$, 3 studies	0.86 (0.08, 8.79), $P = 0.29$, $I^2 = 11\%$, 2 studies
Recurrence (OR)	0.24 (0.10, 0.57), $P = 0.001$, $I^2 = 0$, 3 studies	0.14(0.02,0.72), $P = 0.01$, $I^2 = 11\%$, 2 studies
R0 resection (OR)	1.62 (0.86, 3.04), $P = 0.15$, $I^2 = 52$, 2 studies	1 study
Total complications (RR)	0.70 (0.48, 1.03), $P = 0.07$, $I^2 = 12\%$, 7 studies	2.17 (0.77, 6.17), $P = 0.15$, $I^2 = 0\%$, 3 studies
Intra-procedural bleeding (RR)	0.64 (0.44, 0.94), $P = 0.02$, $I^2 = 0\%$, 7 studies	0.85 (0.15, 4.73), $P = 0.85$, $I^2 = 74\%$, 4 studies
Delayed bleeding (RR)	0.95 (0.35, 2.60), $P = 0.93$, $I^2 = 0\%$, 7 studies	1.77 (0.23, 13.34), $P = 0.84$, $I^2 = 0\%$, 3 studies
Perforation (RR)	0.89 (0.14, 5.62), $P = 0.99$, $I^2 = 0\%$, 7 studies	0.89 (0.09, 8.39), $P = 0.92$, $I^2 = 0\%$, 3 studies
Post-polypectomy syndrome (RR)	1.26 (0.30, 5.28), $P = 0.75$, $I^2 = 0\%$, 7 studies	0.92 (0.13, 6.41), $P = 0.93$, $I^2 = 0\%$ 4 studies
En bloc resection (OR)	1.44(0.74, 2.78), $P = 0.28$, $I^2 = 84\%$, 7 studies	0.90 (0.38, 2.17), $P = 0.82$, $I^2 = 58\%$, 5 studies

[1] Results are odds ratio (OR) or relative risk (RR), 95 % confidence interval, I2, P value and number of studies.

In CEMR, increased colonic wall tension and gas insufflation also flattens the target lesion that complicates snare entrapment and can leave residual tissue. In addition, lesion flattening increases its overall surface area that might lead to more piecemeal resection. Underwater, the colon wall is involuted and has less area, thus, snare can potentially target and resect a larger lesion with UEMR. Needle tract seeding is also known risk in several endoscopic procedures and gastrointestinal malignancies [34, 35]. Although rates may vary, there is a risk of submucosal microscopic seeding during submucosal injection in CEMR that can also contribute to higher rate of recurrence.

Submucosal injection in CEMR is performed to prevent deep thermal injury whereas UEMR utilizes natural collapsed state as water submersion decrease colonic wall tension and takes advantage of submucosal layer fat buoyancy which moves away from the muscularis propria, minimizing the risk of complications. In CEMR, needle puncture itself might precipitate bleeding, which possibly explain the significantly less risk of intra-procedural bleeding with UEMR [9]. This benefit of less intra-procedural bleeding was also noticed in non-pedunclated polyps ≥ 10 mm on subgroup analysis. CEMR may also lead to perforation and deep muscle injury if submucosal injection is misdirected. This can also be completely avoided with UEMR. Overall the rate of perforation was very low in both groups but UEMR does have these theoretical advantages. There was only one case of perforation after and 2 cases of perforation in CEMR group. On literature review, there was one additional case of perforation reported after UEMR whereas perforation rate of CEMR ranges from 0.8 to 1.5 % [36, 37]. In our study, there was no significant difference in rates of delayed bleeding, perforation and PPS between both groups.

UEMR has also been shown reported to have less procedure time as compared to CEMR [26]. Although we were not able to directly compare the duration of procedure due to non-uniformity of data, but there was trend of less procedural time with UEMR. The UEMR duration ranged from 1.5 minutes to 13.3 minutes whereas CEMR duration ranged from 2.9 minutes to 26.1 minutes. The less duration in UEMR is possibly explained by decreased rate of intra-procedural bleeding and absence of submucosal injection. CEMR is considered technically challenging on the right-sided lesions especially around appendiceal orifice due to thin wall and lack of muscularis mucosa. UEMR has also shown good results in resection of lesions at ileocecal valve and appendiceal orifice [11, 38]. UEMR might also be valuable technique in tackling recurrent lesions. In one study comparing UEMR and CEMR, UEMR was superior in terms of higher rate of en bloc resection and fewer adenoma recurrences [39]. In fact, the rate of en bloc resection was almost 50 % in that study, which is also comparable to ESD [39, 40].

ESD is considered as treatment of choice for lesions greater than 20 mm with Paris IIc or IIa + IIc morphology or for any lesions greater than 3 cm per Japanese guidelines [41]. ESD is, however, limited by its high complications rate of 2 % to 14 % [36]. ESD is also technically challenging and time consuming, requires more training even by experienced endoscopists [2, 42, 43]. UEMR can be easily learned and grasped by endoscopist's experienced in CEMR and can have quick uptake in the community practice.

Our review has many strengths including systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good quality studies with detailed extraction of data and rigorous evaluation of study quality. The previous systematic review on UEMR did not provide data on non-pedunculated polyps and direct comparison between UEMR and CEMR [44]. There are limitations to this review, most of which are inherent to any meta-analysis. The studies were representative of centers in North and South America, Asia and Europe and not restricted to a geographic location. However, these studies were not entirely representative of the general population and community practice, with most studies being performed in tertiary-care referral centers. Our analysis had studies that were retrospective in nature contributing to selection bias and confounding bias. Although likely minimal, we could not account for intra-class correlation. The sample size of non-pedunculated polyps >20 mm included in our study is small. Nevertheless, our study is the best available estimate in literature thus far, with respect to the clinical outcomes comparing UEMR and CEMR for resection of colorectal polyps.

Conclusion

In conclusion, our meta-analysis demonstrates that UEMR is associated with higher rate of complete resection and significantly fewer rate of recurrence. UEMR is also associated with significantly lower rates of adverse events and intra-procedural bleeding as compared to CEMR. These results were also significant for non-pedunculated polyps >10 mm. In expert hands UEMR could be preferred over CEMR.

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Competing interests

The authors declare that they have no conflict of interest.

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