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 polypektomy [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-polypektomy 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 I² 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 pa-
tients 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 2.3% (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, I²=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, I²=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, I²=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, I²=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, I²=0, P=0.004) (Fig. 2b). There were 16 cases (1.8%) 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, I²=1, P=0.24), perforation (RR: 0.89, 95% CI, 0.14–5.62, I²=0, P=0.90), and PPS (RR: 1.08, 95% CI, 0.11–10.27, I²=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, I²=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, I²=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, I²=55, P=0.11) were not significant but recurrence rate (OR: 0.24, 95% CI, 0.10–0.57, I²=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, I²=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, I²=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, I²=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, I²=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, I²=11%, P=0.29) and en bloc resection (OR: 0.90, 95% CI, 0.38–2.17, I²=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, I²=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, I²=0, P=0.15), intra-procedural bleeding (RR: 0.85, 95% CI, 0.15–4.73, I²=74%, P=0.85), delayed bleeding (RR: 1.77, 95% CI, 0.23–13.34, I²=0%, P=0.84), perforation (RR: 0.89, 95% CI, 0.09–8.39, I²=0, P=0.92), and PPS (RR: 0.92 (95% CI, 0.13–6.41, I²=0, P=0.93). We were unable to compare rate of R0 resection due to only
| 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) |
|------------------------------|------------|--------------------|------------------|---------------------------|------------|----------------------------------------|---------------------|----------------|----------------------------------|
| Liverant et al, 2016 [26]   | Retrospective | 39                 | 32               | 63.4                      | 22         | 17.2 (2–60)                            | NR                  | NR             | 46 64 NR                        |
| Cadoni et al, 2017 [24]     | Retrospective | 141                | 146              | 65.2                      | 52         | 10.3                                  | 108 112             | 23.1 19.4       | median 3.4 median 1.5            |
| Chien et al, 2017 [13]      | Retrospective | 108                | 115              | 64.2 ± 10                 | 45         | 16.6 ± 6.5                            | 57.8 53.7           | 10.8 ± 8.3 8.6 ± 6.4 |
| Schenck et al, 2017 [28]    | Retrospective | 53                 | 46               | 62.3                      | 18         | 21.9                                  | 82.3 67.1           | NR NR          |
| Hamerski et al, 2018 [25]   | RCT         | 179 total          | 88               | 67.7 overall1             | 90 total1  | 28.1                                  | 81.5 total2         | 18.4 10.2       |
| Rodriguez-Sanchez et al, 2019 [27] | Prospective | 137 total1         | 112 total1       | 66.25 ± 10.53 overall1    | 56 total1  | 30.38                                 | 52.6 76             | 26.14 9.82      |
| Yamashina et al, 2019 [29]  | RCT         | 102 108            | 102 108          | 68                        | 70         | 44                                     | 102 108             | 66.6 61.1       | median 2.91 median 2.75         |
| Mouchli et al, 2019 [30]    | Retrospective | 122                | 68               | 64.4 ± 10                 | 59         | NR XR                                  | NR XR               | NR XR          |
| Yen et al, 2019 [31]        | RCT         | 127 128            | 501              | 64.6 ± 8.3                | 5          | 9.9 ± 5.8                             | 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                          | CEMR | UEMR | CEMR | UEMR | 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   | 14   | 3/20 | 0/16 |
| 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   | 6.1  | 13/46 | 4/55 |
| Schenck et al, 2017 [28]       | 22   | 21   | 8    | 1    | NR   | NR   | 0    | 3    | 0    | 0    | 0    | 3    | 0    | 0    | 0    | 0    | 1    | 6   | 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   | 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.
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 I2 percentage values. The I2 tell us what proportion of the dispersion is true vs. chance [20]. The I2 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.
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 | Conventional EMR Events | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------------------|-----------------------|-------------------------|--------|-----------------------------|-----------------------------|
| Cadoni et al., 2017       | 2                     | 1                       | 9.7%   | 1.91 [0.17, 20.86]           |
| Chien et al., 2017        | 1                     | 1                       | 7.3%   | 1.00 [0.06, 15.81]           |
| Hamerski et al., 2018     | 1                     | 4                       | 11.8%  | 0.24 [0.03, 2.12]            |
| Liverant et al., 2016     | 2                     | 4                       | 10.0%  | 2.46 [0.23, 26.15]           |
| Mouchli et al., 2019      | 6                     | 3                       | 30.4%  | 3.59 [0.93, 13.89]           |
| Rodriguez-Sanchez et al., 2019 | 0                 | 4                       | 6.6%   | 0.25 [0.01, 4.49]            |
| Schenck et al., 2017      | 3                     | 0                       | 6.4%   | 5.96 [0.31, 113.19]          |
| Yamashina et al., 2019    | 3                     | 2                       | 17.8%  | 1.42 [0.24, 8.31]            |
| Yen et al., 2019          | 0                     | 0                       | 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)

---

**Study or Subgroup**

| Study or Subgroup          | Underwater EMR Events | Conventional EMR Events | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------------------|-----------------------|-------------------------|--------|-----------------------------|-----------------------------|
| Cadoni et al., 2017       | 0                     | 1                       | 33.3%  | 3.00 [0.12, 72.92]           |
| Chien et al., 2017        | 1                     | 1                       | 33.3%  | 0.32 [0.01, 7.81]            |
| Hamerski et al., 2018     | 0                     | 1                       | 33.3%  | Not estimable               |
| Liverant et al., 2016     | 0                     | 1                       | Not estimable |                             |
| Rodriguez-Sanchez et al., 2019 | 0                 | 1                       | 33.4%  | 0.74 [0.03, 17.82]           |
| Schenck et al., 2017      | 0                     | 1                       | Not estimable |                             |
| Yamashina et al., 2019    | 0                     | 1                       | Not estimable |                             |
| Yen et al., 2019          | 0                     | 0                       | 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)

---

**Study or Subgroup**

| Study or Subgroup          | Underwater EMR Events | Conventional EMR Events | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------------------|-----------------------|-------------------------|--------|-----------------------------|-----------------------------|
| Cadoni et al., 2017       | 0                     | 1                       | 49.8%  | 2.90 [0.12, 70.30]           |
| Chien et al., 2017        | 0                     | 1                       | 50.2%  | 0.41 [0.02, 9.75]            |
| Hamerski et al., 2018     | 1                     | 1                       | Not estimable |                             |
| Liverant et al., 2016     | 0                     | 1                       | Not estimable |                             |
| Rodriguez-Sanchez et al., 2019 | 0                 | 1                       | Not estimable |                             |
| Schenck et al., 2017      | 0                     | 1                       | Not estimable |                             |
| Yamashina et al., 2019    | 0                     | 1                       | Not estimable |                             |
| Yen et al., 2019          | 0                     | 0                       | Not estimable |                             |
| Total (95% CI)            | 745                   | 769                     | 100.0% | 1.08 [0.11, 10.27]           |

**Total events**
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)

---

**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.
In CEMR, increased colonic wall tension and gas insufflation also flattens the target lesion that complicates snare entrapment and can lead to 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-pedunculated polyps ≥ 10 mm comparing conventional endoscopic mucosal resection and underwater endoscopic submucosal resection.

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-pedunculated polyps ≥ 10 mm comparing conventional endoscopic mucosal resection and underwater endoscopic submucosal resection.

| Nonpedunculated polyps ≥ 10 mm | Nonpedunculated polyps ≥ 20 mm |
|-------------------------------|-------------------------------|
| Incomplete resection (OR)     | 0.26 (0.03, 2.54), P=0.11, I²= 55 %, 3 studies |
| Recurrence (OR)               | 0.24 (0.10, 0.57), P=0.001, I²= 0 %, 3 studies |
| R0 resection (OR)             | 1.62 (0.86, 3.04), P=0.15, I²= 52, 2 studies |
| Total complications (RR)      | 0.70 (0.48, 1.03), P=0.07, I²= 12 %, 7 studies |
| Intra-procedural bleeding (RR) | 0.64 (0.44, 0.94), P=0.02, I²= 0 %, 7 studies |
| Delayed bleeding (RR)         | 0.95 (0.35, 2.60), P=0.93, I²= 0 %, 7 studies |
| Perforation (RR)              | 0.89 (0.14, 5.62), P=0.99, I²= 0 %, 7 studies |
| Post-polypectomy syndrome (RR)| 1.26 (0.30, 5.28), P=0.75, I²= 0 %, 7 studies |
| En bloc resection (OR)        | 1.44(0.74, 2.78), P=0.28, I²= 84 %, 7 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-pedunculated polyps ≥ 10 mm comparing conventional endoscopic mucosal resection and underwater endoscopic submucosal resection.

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, 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].}

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.
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.

Acknowledgement

The authors thank medical librarian Marian T. Simonson, MSLS, AHIP for assisting us in literature search.

Competing interests

The authors declare that they have no conflict of interest.

References

[1] Burgess NG, Bahin FF, Bourke MJ. Colonic polypectomy (with videos). Gastrointest Endosc 2015; 81: 813–835
[2] Gaglia A, Sarkar S. Evaluation and long-term outcomes of the different modalities used in colonic endoscopic mucosal resection. Ann Gastroenterol 2017; 30: 145–151
[3] 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
[4] Jayanna M, Burgess NG, Singh R et al. Cost analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. Clin Gastroenterol Hepatol 2016; 14: 271–278 e271–272
[5] 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
[6] Fukami N, Lee JH. Endoscopic treatment of large sessile and flat colorectal lesions. Curr Opin Gastroenterol 2006; 22: 54–59
[7] Moss A, Williams SJ, Hourigan LF et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colorectal mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut 2015; 64: 57–65
[8] 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
[9] Nett A, Binmoeller K. Underwater endoscopic mucosal resection. Gastrointest Endosc Clin N Am 2010; 20: 659–673
[10] Binmoeller KF. Underwater EMR without submucosal injection: Is less more? Gastrointest Endosc 2019; 89: 1117–1119
[11] Binmoeller KF, Hamerski CM, Shah JN et al. Underwater EMR of adenomas of the appendicular orifice (with video). Gastrointest Endosc 2016; 83: 638–642
[12] Binmoeller KF, Hamerski CM, Shah JN et al. Attempted underwater en bloc resection for large (2–4 cm) colorectal laterally spreading tumors (with video). Gastrointest Endosc 2015; 81: 713–718
[13] Chien H-C, Uedo N, Hsieh P-H. Comparison of underwater and conventional endoscopic mucosal resection for removing sessile colorectal polyps: a propensity-score matched cohort study. Endosc Int Open 2019; 07: E1528–E1536
[14] Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. Ann Int Med 2009; 151: 264–269
[15] Stroup DF, Berlin JA, Morton SC et al. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000; 283: 2008–2012
[16] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Europ J Epidemiol 2010; 25: 603–605
[17] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7: 177–188
[18] Higgins J, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J Royal Stati Society 2009; 172: 137–159
[19] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. Br Med J 2011; 342: d549
[20] Mohan BP, Adler DG. Heterogeneity in systematic review and meta-analysis: how to read between the numbers. Gastroenterost Endosc 2019; 89: 902–903
[21] Kanwal F, White D. Systematic reviews and meta-analyses. Clin Gastroenterol Hepatol 2012; 10: 1184–1186
[22] Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. Br Med J 2003; 327: 557
[23] Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 7 Rating the quality of evidence and inconsistency. J Clin Epidemiol 2011; 64: 1294–1302
[24] The Nordic Cochrane Centre TCC. Review Manager (RevMan) [Computer program], Version 5.3. Copenhagen; 2014
[25] Cadoni S, Liggi M, Gallitello P et al. Underwater endoscopic colorectal polyp resection: Feasibility in everyday clinical practice. United European Gastroenterol J 2018; 6: 454–462
[26] Hamerski CM, Wang AY, Amato A et al. 121 Injection-Assisted versus conventional endoscopic mucosal resection without injection for the treatment of colorectal laterally spreading tumors: interim analysis of an international multicenter randomized controlled trial. Gastrointest Endosc 2018; 87: A855–A856
[27] Liverant ML, Yip B, Kwak N et al. Su1690 Underwater Endoscopic mucosal resection (EMR) shows a higher single session curative resection rate than conventional EMR technique: a single center experience. Gastrointest Endosc 2016; 83: A8397
[28] Rodriguez Sanchez J, Uchima Koecklin H, Gonzalez Lopez L et al. Short and long-term outcomes of underwater EMR compared to the traditional procedure in the real clinical practice. Rev Esp Enferm Dig 2019; 111: 543–549
[29] Schenck RJ, Jahann DA, Pattrie JT et al. Underwater endoscopic mucosal resection is associated with fewer recurrences and earlier curative resections compared to conventional endoscopic mucosal resection for large colorectal polyps. Surg Endosc 2017; 31: 4174–4183
[30] Yamashina T, Uedo N, Akasaka T et al. Comparison of underwater vs conventional endoscopic mucosal resection of intermediate-size colorectal polyps. Gastroenterology 2019; 157: 451–461 e452
[31] Mouchli M, Walsh C, Reddy S et al. Sa1727 – Outcomes of gi polyps resected using underwater endoscopic mucosal resection (UEMR)
Compared to conventional EMR (CEMR). Gastroenterology 2019; 156: S379–S380

[32] Yen AW, Leung JW, Wilson MD et al. Underwater versus conventional endoscopic resection of nondiminutive nonpedunculated colorectal lesions: a prospective randomized controlled trial (with video). Gastrointest Endosc 2020; 91: 643–654 e642

[33] 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

[34] Silva MA, Hegab B, Hyde C et al. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut 2008; 57: 1592–1596

[35] Yokoyama K, Ushio J, Numao N et al. Esophageal seeding after endoscopic ultrasound-guided fine-needle aspiration of a mediastinal tumor. Endosc Int Open 2017; 5: E913–E917

[36] Nakajima T, Saito Y, Tanaka S et al. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc 2013; 27: 3262–3270

[37] Ponugoti PL, Rex DK. Perforation during underwater EMR. Gastrointest Endosc 2016; 84: 543–544

[38] Levy I, Hamerski CM, Nett AS et al. Su1618 underwater endoscopic mucosal resection (UEMR) of laterally spreading tumors involving the ileocecal valve. Gastrointestinal Endoscopy 2017; 85: AB366

[39] 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

[40] Sakamoto T, Matsuda T, Otake Y et al. Predictive factors of local recurrence after endoscopic piecemeal mucosal resection. J Gastroenterol 2012; 47: 635–640

[41] Tanaka S, Kashida H, Saito Y et al. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc 2015; 27: 417–434

[42] Saito Y, Uraoka T, Yamaguchi Y et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc 2010; 72: 1217–1225

[43] Uraoka T, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection: is it suitable in western countries? J Gastroenterol Hepatol 2013; 28: 406–414

[44] Spadaccini M, Fuccio L, Lamonaca L et al. Underwater EMR for colorectal lesions: a systematic review with meta-analysis (with video). Gastrointest Endosc 2019; 89: 1109–1116 e1104