

Is underwater endoscopic mucosal resection of colon polyps superior to conventional techniques? A network analysis of endoscopic mucosal resection and submucosal dissection




Authors

Darren Jun Hao Tan¹, Cheng Han Ng¹, Xiong Chang Lim¹, Wen Hui Lim¹, Linus Zhen Han Yuen¹, Jin Hean Koh¹, Kameswara Rishi Yeshayahu Nistala¹, Khek-Yu Ho^{1,2}, Choon Seng Chong^{*,3}, Mark D. Muthiah^{*,1,2}

Institutions

- 1 Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
- 2 Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore, Singapore
- 3 Division of Colorectal Surgery, Department of Surgery, National University Hospital, Singapore, Singapore

submitted 21.3.2021

accepted after revision 11.8.2021

Bibliography

Endosc Int Open 2022; 10: E154–E162

DOI 10.1055/a-1633-3230

ISSN 2364-3722

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author

Dr. Mark Muthiah, MBBS (S'pore), MRCP (UK), MMED (S'pore), Consultant Gastroenterologist and Hepatologist, Division of Gastroenterology and Hepatology, Tower Block Level 10, 1E Kent Ridge Road, 119228, Singapore
Phone: +65 6772 4354
mdcmdm@nus.edu.sg

 Supplementary material is available under
<https://doi.org/10.1055/a-1633-3230>

ABSTRACT

Background and study aims Evidence from recent trials comparing conventional endoscopic mucosal resection (EMR) to underwater EMR (UEMR) have matured. However, studies comparing UEMR to endoscopic submucosal dissection (ESD) are lacking. Hence, we sought to conduct a comprehensive network meta-analysis to compare the efficacy of UEMR, ESD, and EMR.

Methods Embase and Medline databases were searched from inception to December 2020 for articles comparing UEMR with EMR and ESD. Outcomes of interest included rates of en bloc and complete polyp resection, risk of perforation and bleeding, and local recurrence. A network meta-analysis comparing all three approaches was conducted. In addition, a conventional comparative meta-analysis comparing UEMR to EMR was performed. Analysis was stratified according to polyp sizes (<10 mm, ≥10 mm, and ≥20 mm).

Results Twenty-two articles were included in this study. For polyps ≥10 mm, UEMR was inferior to ESD in achieving en bloc resection ($P=0.02$). However, UEMR had shorter operating time for polyps ≥10 mm ($P<0.001$), and ≥20 mm ($P=0.019$) with reduced perforation risk for polyps ≥10 mm ($P=0.05$) compared to ESD. In addition, en bloc resection rates were similar between UEMR and EMR, although UEMR had reduced recurrence for polyps ≥10 mm ($P=0.013$) and ≥20 mm ($P=0.014$). UEMR also had shorter mean operating than EMR for polyps ≥10 mm ($P<0.001$) and ≥20 mm ($P<0.001$). Risk of bleeding and perforation with UEMR and EMR were similar for polyp of all sizes.

Conclusions UEMR has demonstrated technical and oncological outcomes comparable to ESD and EMR, along with a desirable safety profile. UEMR appears to be a safe and effective alternative to conventional methods for resection of polyps ≥10 mm.

* These authors contributed equally

Introduction

Colorectal cancer is the second most deadly cancer worldwide, accounting for 10% of deaths annually [1]. Current prevention strategies entail endoscopic resection of precancerous lesions [2] and recent advancements in endoscopic techniques have improved the rate of en bloc resection, amounting to decreased recurrence rates over the last decade. In particular, the use of underwater endoscopic mucosal resection (UEMR) has gained notability for its perceived benefits [3]. UEMR was first conceived by Binmoeller et al in 2012 and has since been replicated in many centers [4]. The procedure involves insufflation of the lumen with water prior to polyp removal, which has been perceived to allow for easier resection of polyps and reduced risk of thermal injury. Conventionally, resection of polyps has been done via endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), with evidence from meta-analysis favoring the later in larger lesions. The European Society of Gastrointestinal Endoscopy (ESGE) consensus recommended the use of ESD in lesions >20 mm [5]; however, the steep learning curve has limited its application in the West [6]. While evidence from randomized controlled trials comparing UEMR and EMR has matured [7, 8], the potential to outperform ESD has yet to be established.

At present, there have been a number of meta-analyses focusing on single-arm outcomes of UEMR and its relative efficacy compared to EMR. However, many of these studies were conducted in fixed-effect models, which have since been subjected to skepticism due to mounting evidence for use of random effects models [9]. In addition, the utility of UEMR and EMR in lesions <10 mm has yet to be evaluated. Thus, we performed: (1) a conventional pairwise meta-analysis to compare between UEMR and EMR with random effects models and subgroup analysis for different polyp sizes; and (2) network analysis to compare the efficacy of UEMR vs ESD and UEMR vs EMR.

Methods

Search strategy

This review was synthesized according to PRISMA guidelines. A search was conducted on Medline and Embase for articles comparing UEMR with conventional techniques (ESD, EMR) on December 2, 2020. The search strategy used was “underwater adj3 (endoscop* mucosal resect*) or UEMR” in titles and abstracts. References were downloaded into Endnote X9 and duplicates were removed. We previously conducted a meta-analysis comparing ESD and EMR on October 4, 2020 [10] and the data were used to supplement the network meta-analysis.

Inclusion criteria and data extraction

Two authors (DJHT, CHN) screened references for suitability based on abstracts. We included randomized controlled trials (RCTs) and retrospective and prospective cohort studies that compared UEMR with conventional techniques. Only original articles were included and editorials, commentaries and reviews were excluded. Two authors in a blinded pair (DJHT, CHN) extracted relevant raw data into a structured proforma.

The main outcomes evaluated were rates of en bloc resection, complete resection, perforation, bleeding, operation time, and recurrence. En bloc resection was defined as endoscopically confirmed removal of a polyp in a single piece, while complete resection was defined either with histologically confirmed negative margins or absence of macroscopically visible polyp fragments. Bleeding events were analyzed as a summative of intra-procedural and delayed bleeding. As with previous reviews, recurrence rate was extracted from the last recorded follow-up [3, 11–16]. Unreported means and standard deviations were converted using pre-existing formulas by Wan et al [17].

Statistical analysis

First, a conventional pairwise meta-analysis was conducted using the Dersimonian and Laird model. Dichotomous variables were analyzed in risk ratios (RR), and continuous variables in weighted mean difference (WMD). Fixed effect models have many assumptions beyond statistical significance in heterogeneity and many have advocated for use of random effects in meta-analysis [9]. Thus, all analysis was conducted with random effects model regardless of heterogeneity (Tau², I², and Cochran Q test). For outcomes where sufficient data was available, prediction intervals were also calculated [18]. Subgroup analysis was considered according to lesion size (<10mm, ≥10mm and ≥20mm).

In the network meta-analysis, a frequentist approach as described by Ian White [19] was used in the estimation of effect size for indirect comparisons. Only articles with polyps ≥10mm were considered, with sensitivity analysis for ≥20mm. Recurrence was not included in the network analysis due to significantly different follow-up times between EMR vs ESD and EMR vs UEMR (4.9 vs 22.0 months). The network analysis was done in the natural log of RR and the results were exponentiated for conversion back to RR. Inconsistency testing, which quantifies that results are sufficiently similar for an indirect comparison to be drawn, was done through both local and global approaches using Wald's test and node splitting [19]. Publication bias was evaluated through visual inspection of funnel plots. All analysis was conducted in STATA 16.1, or R Studio (version 4.0.3) using the meta package where appropriate. Statistical significance was considered at P<0.05 for all outcomes.

Quality assessment and risk of bias

RCTs were assessed by the Cochrane Risk-of-Bias 2.0 tool for appropriateness of randomization process, deviation from intended outcomes, missing data, measures of outcomes, and selection of reporting [20]. Non-randomized studies were analyzed with the Newcastle-Ottawa Scale (NOS) [21], which is designed to assess such studies in three domains: (1) selection of the study groups; (2) comparability of the groups; and (3) outcome of interest for cohort studies. Studies with NOS scores of 7–9, 4–6, and <3 were interpreted as having low, moderate, and high risk of bias respectively.

Results

Summary of included articles

A total of 194 articles were included in the initial search, with 145 remaining after duplicate removal (► **Fig. 1**). Thirteen articles from a meta-analysis we previously conducted comparing ESD and EMR were manually added [10]. After screening of abstracts, 22 articles were included in both groups of analysis [7, 8, 22–41]. The network analysis comprised 13 articles for ESD and EMR [29–41] and eight studies comparing UEMR with EMR [7, 8, 22–26, 28]. Seven studies were conducted in Japan [7, 29–32, 34, 37], four in the United States [8, 23, 25, 26], three in Korea [33, 35, 41], and one each in China [27], Czech Republic [40], France [39], Italy [36], Spain [22], Taiwan [28], and the United Kingdom [38]. One included study [24] was a multicenter trial involving centers in Italy and the United States. There were four RCTs, with the remaining being cohort studies. **Supplementary material 1** summarizes the characteristics of included studies, including the risk of bias and quality assessment for RCTs and non-randomized studies respectively. In brief, four of the non-randomized studies included in the analysis had a NOS score >7, representing a low risk of bias, while the remaining non-randomized study had a NOS score of 6, corresponding to a moderate risk of bias. In addition, all the included RCTs had low concern for risk of bias as assessed via the Cochrane Risk-of-Bias 2.0 tool, with the exception of one study done by Hamerski et al [24], which demonstrated possible sources of bias from incomplete reporting of data.

Comparative (pairwise) meta-analysis

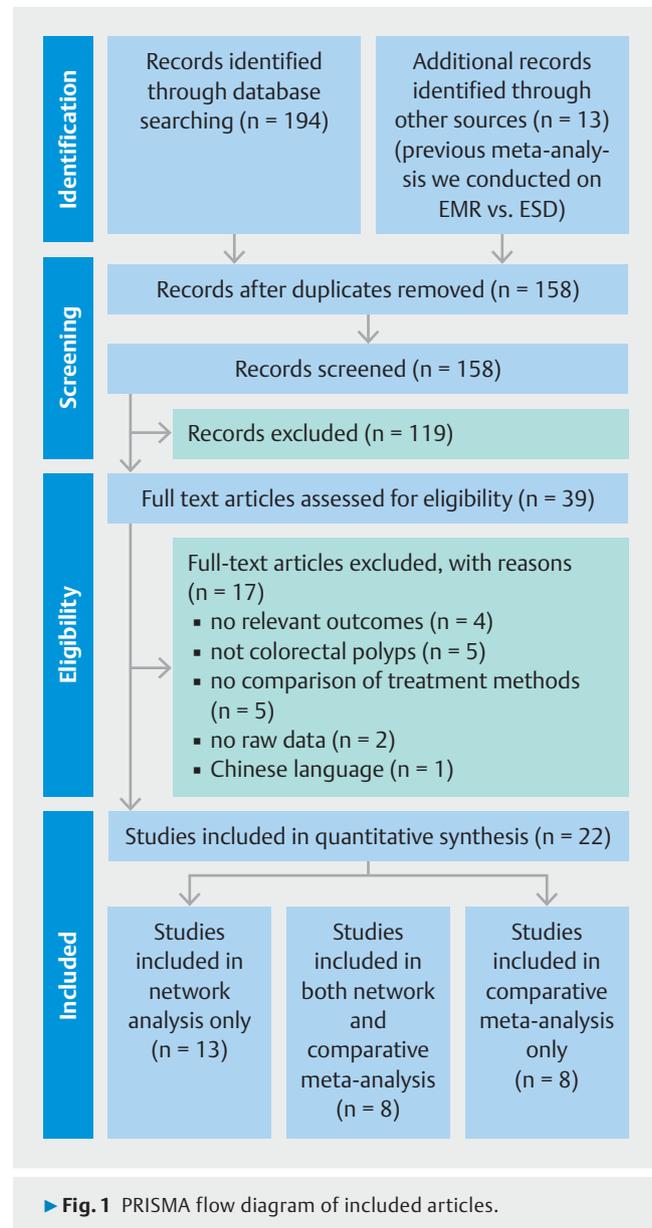
A total of 1,551 polyps were included for pairwise analysis of UEMR and EMR. A total of 733 polyps were resected via UEMR while 818 polyps were removed using conventional EMR. A summary of the results is presented in ► **Table 1** and a summary of the prediction intervals in included in **Supplementary material 3**.

Polyps < 10 mm

Pooled analysis of 486 polyps < 10 mm revealed no statistically significant differences between UEMR and EMR in achieving en bloc (RR: 0.992, CI: 0.740–1.330, $P=0.955$, ► **Fig. 2**) and complete resection (RR: 0.999, CI: 0.768–1.299, $P=0.973$). Interestingly, pooled analysis demonstrated that UEMR had longer operating time than EMR (WMD: 0.162 mins, CI: 0.102–0.223 minutes, $P<0.001$). There was no statistically significant difference in perforation and bleeding for polyps < 10 mm.

Polyps ≥ 10 mm

From pooled analysis of 1,170 polyps, there was no statistically significant difference between UEMR and EMR in terms of en bloc resection (RR: 1.197, CI: 0.922–554, $P=0.137$, prediction interval: 0.699–2.050, ► **Fig. 2**) and complete resection (RR: 1.122, CI: 0.906–1.389, $P=0.185$, prediction interval: 0.505–2.492). Pooled analysis of 1,409 polyps also demonstrated that UEMR was associated with shorter procedure times (WMD: –1.364 mins, CI: –1.754 to –0.975 minutes, prediction interval –15.458 to 5.627, $P<0.001$). UEMR was also associated



with lower recurrence (RR: 0.517, CI: 0.286–0.935, $P=0.036$, prediction interval: 0.240–1.116). There was no statistically significant difference in perforation and bleeding risk.

Polyps ≥ 20 mm

From analysis of 479 polyps ≥ 20 mm, the difference in rate of en bloc RR: 1.358, CI: 0.624–2.955, $P=0.299$, prediction interval: 0.214–8.636, ► **Fig. 2**) and complete resection (RR: 0.930, CI: 0.793–1.113, $P=0.470$) did not reach statistical significance. UEMR continued to be associated with shorter operating time (WMD: –2.253 mins, CI: –2.693 to –1.812 minutes, $P<0.001$). UEMR was also superior in terms of reduced local recurrence after resection of larger polyps (RR: 0.169, CI: 0.053–0.542, $P=0.003$). There was no statistically significant difference in perforation and bleeding.

► **Table 1** Summary of pooled analysis comparing UEMR and EMR.

Outcomes	Total studies	Events	Total sample	Effect size (95% CI)	P
≤ 10 mm					
▪ On-piece resection	2	470	486	0.992 (0.740–1.330)	0.955
▪ Complete resection	2	458	486	0.999 (0.768–1.299)	0.973
▪ Perforation	2	2	486	0.955 (0.528–1.725)	0.500
▪ Bleeding	2	5.5	486	0.367 (0.059–2.275)	0.091
▪ Mean Operation Time	2	NA	486	0.162 mins (0.102 to 0.223)	<0.001
≥ 10 mm					
▪ One-piece resection	6	698	1170	1.197 (0.922–1.554)	0.137
▪ Complete resection	4	517	625	1.122 (0.906–1.389)	0.185
▪ Perforation	7	10.5	1219	1.042 (0.504–2.154)	0.894
▪ Bleeding	8	85.5	1409	1.004 (0.489–2.064)	0.989
▪ Recurrence	5	111	624	0.517 (0.286–0.935)	0.036
▪ Mean Operation Time	5	NA	1409	-1.364 mins (-1.754 to -0.975)	<0.001
≥ 20 mm					
▪ One-piece resection	4	186	479	1.358 (0.624–2.955)	0.299
▪ Complete resection	1	31	32	0.939 (0.793–1.113)	0.470
▪ Perforation	1	1	32	1.000 (0.021–47.380)	1.00
▪ Bleeding	1	5	32	1.500 (0.288–7.807)	0.630
▪ Recurrence	1	15	67	0.169 (0.053–0.542)	0.003
▪ Mean operation time	2	NA	546	-2.253 mins (-2.693 to -1.812)	<0.001
UEMR, underwater endoscopic mucosal resection; EMR, endoscopic mucosal Resection; NA, not applicable.					

Network meta-analysis

The network diagram for the comparison of UEMR vs ESD and UEMR is represented in ► **Fig. 3**. Interval plots of the network analysis are represented in ► **Fig. 4**. Results of the analysis are summarized in ► **Table 2**. For all outcomes, global test of inconsistency and local node splitting did not reveal any significance for inconsistency. No publication bias was observed aside from complete resection and operation time from visual inspection of funnel plots (**Supplementary material 4**). The summary of GRADE evidence can be found in **Supplementary material 5**.

Polyps ≥ 10 mm

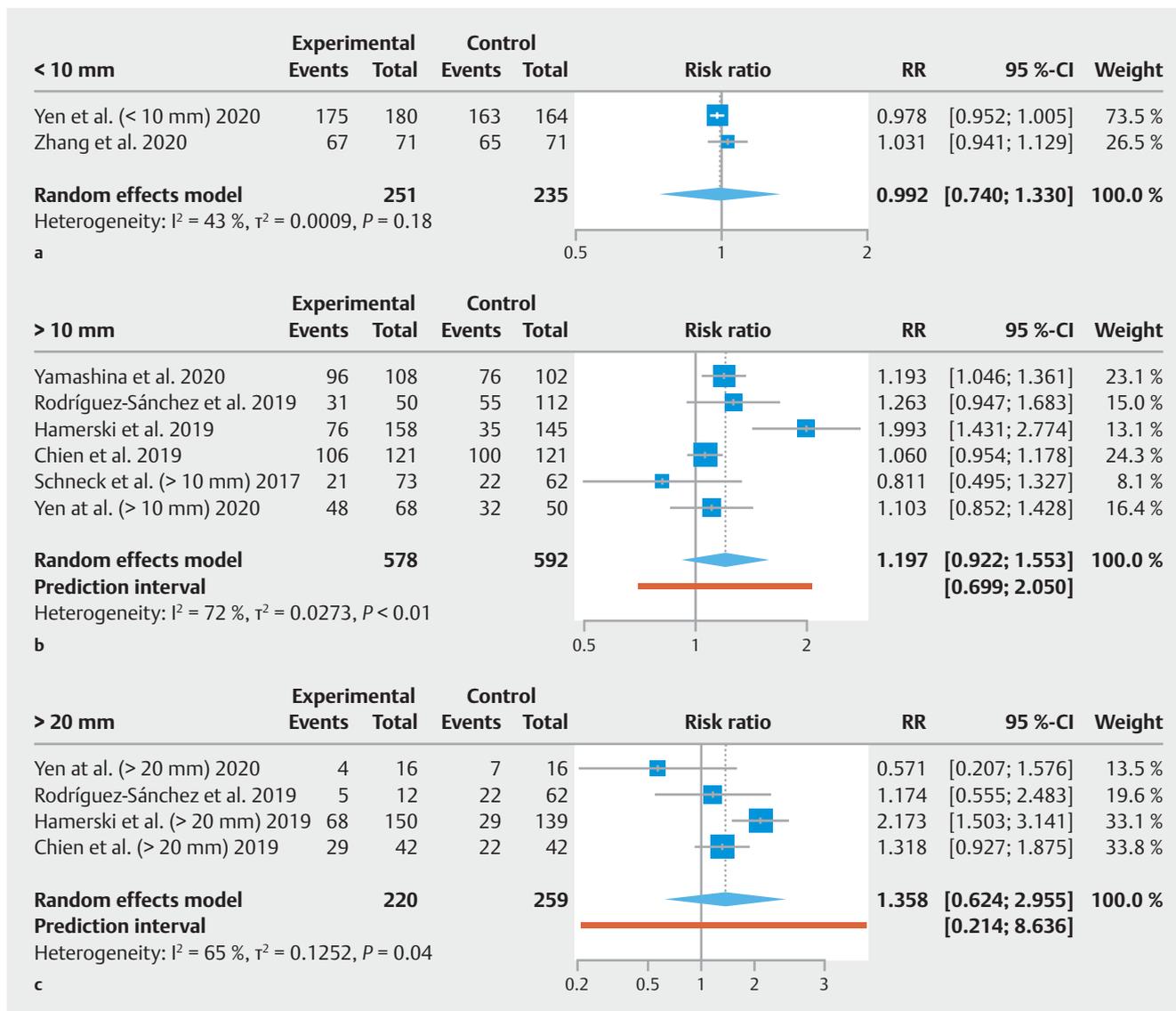
UEMR was found to be inferior to ESD in achieving en bloc resection (RR: 0.645, CI: 0.445–0.934, $P=0.020$). There was no statistically significant difference in achieving complete resection (RR: 0.786, CI: 0.533–1.160, $P=0.226$). UEMR was associated with statistically significantly decreased procedure time compared to ESD (WMD: -69.61 mins, CI: -101.63 to -37.59 minutes, $P<0.001$). UEMR was also associated with reduced risk of perforation (RR: 0.273, CI: 0.0731–1.012, $P=0.05$) but bleeding risk did not significantly differ (RR: 0.89, CI: 0.35–2.28, $P=0.807$).

Comparing UEMR and EMR via network analysis, there was no statistically significant difference for en bloc (RR: 1.200, CI: 0.902–1.595, $P=0.211$) and complete resection (RR: 1.132, CI: 0.836–1.533, $P=0.423$) of polyps ≥ 10 mm. There were no statistically significant differences in perforation (RR: 1.141 CI: 0.336–3.874, $P=0.832$) and bleeding (RR: 1.049 CI: 0.522–2.107, $P=0.894$) for UEMR and EMR.

Polyps ≥ 20 mm

When sensitivity analysis was conducted for polyps ≥ 20 mm, there was no statistically significant difference between UEMR and ESD in achieving en bloc (RR: 0.698, CI: 0.396–1.230, $P=0.214$) and complete resection (RR: 0.612, CI: 0.245–1.526, $P=0.292$). Operating time was significantly shortened in UEMR (WMD: -52.56 mins, CI: -96.38 to -8.73 mins, $P<0.019$). There was no statistically significant difference for perforation (RR: 0.201, CI: 0.004–9.993, $P=0.421$) and bleeding (RR: 1.606 CI: 0.280–9.207, $P=0.595$) between UEMR and ESD.

Comparing UEMR to EMR, there was no statistically significant difference for en bloc (RR: 1.349, CI: 0.840–2.168, $P=0.215$) and complete resection (RR: 0.941, CI: 0.417–2.123, $P=0.883$) of polyps ≥ 20 mm. UEMR also did not have statistically



► Fig. 2 Forest plot of UEMR vs EMR for en bloc resection stratified by polyp size.

significant benefit in terms of perforation (RR: 1.000 CI:0.021–47.510, $P=1.00$) and bleeding (RR: 1.5 CI:0.288–7.805, $P=0.63$).

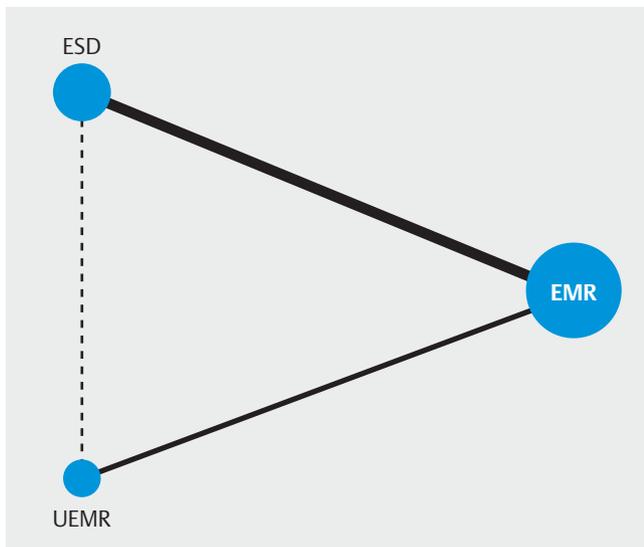
Discussion

Utilizing both conventional pairwise meta-analysis and network meta-analysis, we demonstrated that UEMR might be superior to EMR and ESD for resection of colon polyps ≥ 10 mm, but offered no advantage for polyps < 10 mm. For colon polyps ≥ 10 mm, we demonstrated a significant reduction in procedure time for UEMR compared with both EMR and ESD. UEMR also had a lower recurrence rate than EMR, and a lower risk of perforation as compared to ESD. When comparing UEMR with ESD for polyps ≥ 10 mm, there was a reduced rate of en bloc resection, although rates of complete resection were similar. A further sensitivity analysis for polyps ≥ 20 mm also demonstrated a significant reduction in procedure time with UEMR compared

with both EMR and ESD, and a lower recurrence rate with UEMR as compared to EMR. Only for polyps < 10 mm did UEMR require a longer procedure time than EMR.

These findings have significant implications for delivery of care. We demonstrated the superiority of UEMR in resection of polyps ≥ 10 mm compared to EMR, as improved recurrence rates can lead to reduction in colorectal cancer rates. Compared to ESD, the safety of UEMR, coupled with the reduced procedure times is likely to reduce utilization of healthcare resources. Given the steep learning curve for ESD, use of UEMR may also allow more non-tertiary center-based endoscopists to successfully resect larger colonic polyps, reducing the barrier to care.

UEMR was found to a safety profile similar to conventional methods in terms of perforation and bleeding. The process of underwater emersion increases buoyancy of the lesion, resulting in separation from the muscularis layer and decreasing the risk of adverse events including perforation or deep thermal injury [4, 15]. Also, while the rate of perforation was significant-



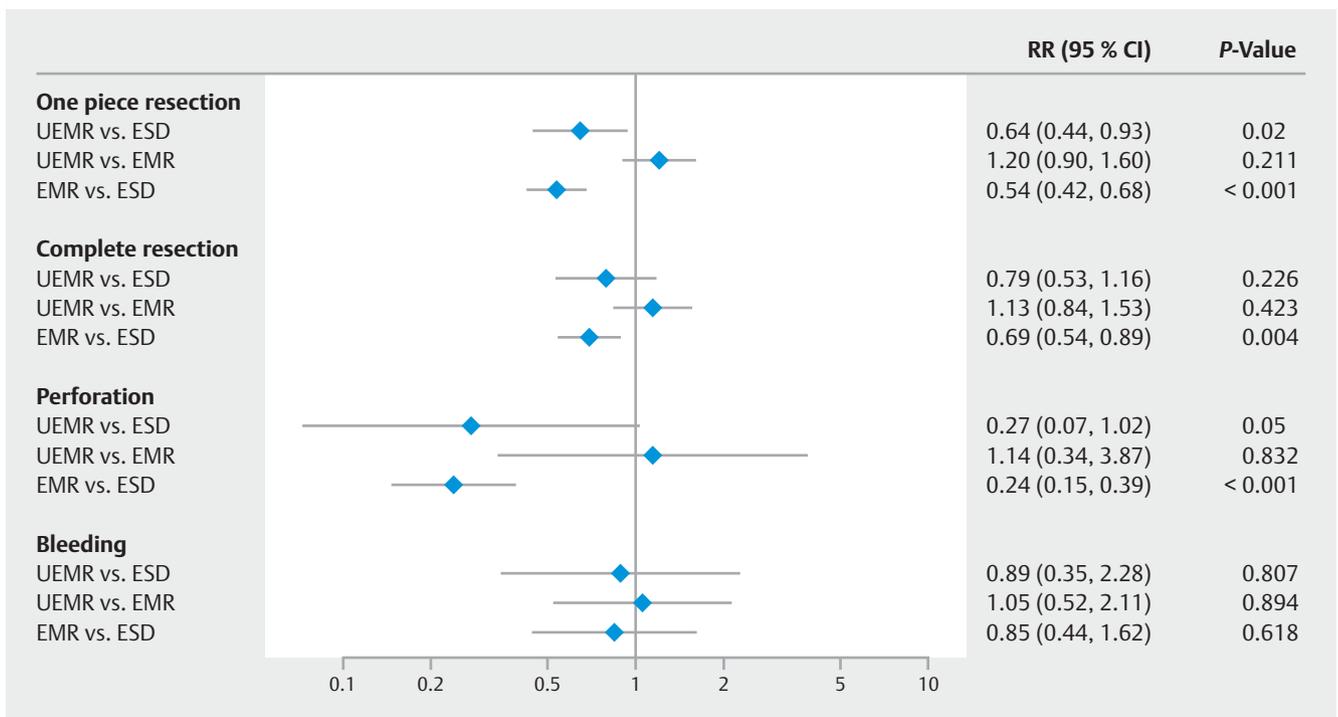
► **Fig. 3** Meta-analysis network diagram.

ly lower compared to that of ESD (RR = 0.273, CI: 0.0731–1.012, $P=0.05$), it was non-significant when studies were limited to ≥ 20 mm. However, the analysis should be interpreted with caution as there were limited studies in UEMR with ≥ 20 mm ($n=2$).

Several previous meta-analyses have studied the comparative benefits of UEMR (**Supplementary material 2**). However, we differ from previous articles with respect to two major points. First, our pairwise analysis between UEMR vs EMR is the first to summarize evidence from polyps < 10 mm, and all other

analyses were performed in fixed effect models. Next, our network analysis is the first to compare the efficacy between UEMR and ESD, as well as to use current knowledge (ESD vs EMR) to supplement the comparisons from UEMR and EMR. A recent meta-analysis by Choi et al [3] found significant improvements in en bloc resection by UEMR, although these results were conducted in fixed effect models (I²: 38%, Cochrane Q: $P=0.14$). Our analysis however found no significant improvement in en bloc resection in both conventional pairwise random effects $P=0.284$) and subsequent network analysis $P=0.423$). In line with existing literature, ESD was found to be superior in achieving en bloc resection for polyps ≥ 10 mm [5]. However, sensitivity analysis for polyps ≥ 20 mm in our network analysis found no significant difference between UEMR and ESD in achieving en bloc resection. This could be the result of the lack of studies for polyps ≥ 20 mm in the UEMR population that could be utilized in the network analysis. Thus, the lack of statistical power could have given rise to non-significance, rather than a non-inferiority in achieving en bloc resection between UEMR and ESD.

Existing literature has demonstrated reduced local recurrence in UEMR compared to EMR [14, 15] and attributed it to higher rates of en bloc resection [42]. In our study, we demonstrated reduced rates of local recurrence with UEMR despite similar rates of en bloc resection compared to EMR. We believe there are additional benefits to UEMR that could have contributed to decreased local recurrence. As noted by Binmoeller et al [4], water immersion results in the lesion floating upwards into the lumen due to increased buoyancy of the mucosal and submucosal layers compared to the underlying muscularis, facilitating snaring of the polyp. Water immersion is also postulated to minimize luminal distention and loop formation [43], and



► **Fig. 4** Forest plot of network analysis comparing UEMR, EMR, and ESD.

► **Table 2** Summary of network analysis comparing UEMR, EMR, and ESD.

	Polyp size ≥ 10 mm		Polyp size ≥ 20 mm	
One-piece resection	Effect size	P value	Effect size	P value
UEMR vs ESD	0.645 CI:0.445–0.934	0.02	0.698 CI:0.396–1.230	0.214
UEMR vs EMR	1.200 CI:0.902–1.595	0.211	1.349 CI: 0.840–2.168	0.215
Complete resection				
▪ UEMR vs ESD	0.786 CI:0.533–1.160	0.226	0.612 CI:0.245–1.526	0.292
▪ UEMR vs EMR	1.132 CI:0.836–1.533	0.423	0.941 CI:0.417–2.123	0.883
Perforation				
▪ UEMR vs ESD	0.273 CI:0.0731–1.012	0.05	0.201 CI:0.004–9.993	0.421
▪ UEMR vs EMR	1.141 CI:0.336–3.874	0.832	1.000 CI:0.021–47.510	1
Bleeding				
▪ UEMR vs ESD	0.889 CI:0.348–2.276	0.807	1.606 CI:0.280–9.207	0.595
▪ UEMR vs EMR	1.049 CI:0.522–2.107	0.894	1.5 CI:0.288–7.805	0.63
Operation Time				
▪ UEMR vs ESD	–69.61 CI:–101.63 to –37.59	<0.001	–52.56 CI:–96.38 to –8.73	0.019
▪ UEMR vs EMR	–2.87 CI:–26.71 to 20.98	0.652	6.30 CI:–28.69 to 41.29	0.515

UEMR, underwater endoscopic mucosal resection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

provides a natural optical magnification effect [42], enabling improved visualization and inspection of residual neoplasia. This is of particular importance for larger polyps as EMR has traditionally been associated with low rates of en bloc resection for polyps ≥ 20 mm and correspondingly high rates of recurrent neoplasia [44].

Due to the significantly different follow-up times for UEMR and ESD (4.9 vs 22.0 months), we did not analyze recurrence rates in the network meta-analysis. However, a previous single-arm analysis estimated a recurrence rate of 9% in UEMR [45], compared to 1% in ESD [46]. Due to advantages in achieving en bloc resection, ESD has the major advantage of decreased recurrence rates compared to other techniques, and UEMR is unlikely to outperform ESD in terms of local recurrence.

Strengths and limitations

To our knowledge, this is the first study that compares UEMR and ESD via a network meta-analysis. This allows for evaluation of outcomes despite a paucity of studies comparing the two treatments. A large sample size of > 1000 polyps was also involved. Finally, we considered outcomes in smaller polyps < 10 mm in the comparison of UEMR vs EMR in order to address heterogeneity possibly arising from differing polyp sizes, which was not included in previous studies. Notwithstanding the rigorous search strategy and statistical methodology, we are limited by the lack of reporting of follow-up duration in several included studies which can affect long term outcomes (e.g. recurrence). The procedures described are also operator-dependent and we were unable to quantify the skills of individual

endoscopists. In addition, due to the limited number of mature clinical trials, we included data from cohort studies in our network analysis, and confounding factors from the selection of patients could have led to biased estimates. However, consistency was not violated throughout the analysis, as shown via node splitting and Wald's test, demonstrating that the results were sufficiently statistically homogenous for an indirect comparison to be made. Finally, we could not account for heterogeneity due to colonoscope models or snare types used in different centers due to a scarcity in reporting. The definition of complete resection also varied with some articles defining it based on visual inspection.

Conclusions

There was no statistically significant benefit of conventional methods in achieving technical outcomes, including one-piece and complete resection, in comparison to UEMR. Combined with the significantly reduced procedural time for UEMR, decreased concern for perforation, and shorter training period to achieve proficiency, this study provides evidence that UEMR is a viable and safe alternative for resection of colonic polyps.

Competing interests

The authors declare that they have no conflict of interest.

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