How to increase proximal adenoma detection rate: a meta-analysis comparing water exchange, water immersion and air/CO₂ insufflation methods for colonoscopy

Muhammad Aziz, Sachit Sharma, Rawish Fatima, Wade Lee-Smith, Thomas Sodeman, Ali Nawras, Douglas G. Adler

University of Toledo Medical Center, Ohio; University of Toledo Libraries, Ohio; University of Utah, Salt Lake City, USA

Abstract

Background Recent meta-analyses have demonstrated a higher adenoma detection rate using the water exchange method (WE), compared to water immersion (WI) and air/CO₂ insufflation (ACI). Proximal adenomas have a high miss rate owing to their location and appearance. We performed a systematic review and meta-analysis of studies comparing the WE and WI methods to the ACI method, with a primary focus on proximal adenoma detection rate.

Methods The following databases were searched for our systematic review: Medline, Embase, Cochrane Library, CINAHL, and Web of Sciences. We included both randomized controlled trials and cohort studies. The primary outcome was proximal adenoma detection rate, and secondary outcomes were right adenoma detection rate and cecal intubation rate.

Results A total of 12 studies (17 arms) with 5660 patients (2260 ACI, 2281 WE, and 1119 WI) were included. A higher proximal adenoma detection rate (risk ratio [RR] 1.30, 95% confidence interval [CI] 1.11-1.53; P=0.001) and right adenoma detection rate (RR 1.43, 95%CI 1.19-1.71; P≤0.001; I²=0%) were noted for the WE group compared to the ACI group. The WI group did not demonstrate a better detection rate of proximal or right adenomas.

Conclusions The water exchange method for colonoscopy holds promise and should be encouraged in the clinical setting to increase proximal and right adenoma detection rates. This will in turn decrease the incidence of colorectal cancer.

Keywords Colonoscopy, proximal adenoma detection rate, right adenoma detection rate, water exchange, water immersion

Ann Gastroenterol 2020; 33 (2): 178-186

Introduction

Recent years have seen the development of 2 water-aided methods, water exchange (WE) and water immersion (WI), for performing colonoscopy [1,2]. Cadoni et al defined the WE method as "a standardized technique that, through infusion and nearly simultaneous suction of water, entails substituting all colon content with a layer of clear water allowing gasless instrument progression to the cecum, minimizing distention, and maximizing cleanliness during insertion" [3]. These authors also defined the WI method as "a technique in which water is infused to facilitate cecal intubation, with limited use of insufflation when necessary. Opaque water is removed as needed to aid progression without maximizing cleanliness. Residual air pockets are used to bypass dirty content" [3]. The infused water is removed during the insertion phase in the WE method and during the withdrawal phase in the WI method [1-3]. Gas insufflation is used for the withdrawal phase in both water-aided methods [3].

Advantages of water-aided methods during colonoscopy potentially include less abdominal distension, improved mucosal visualization, and a higher rate of achieving cecal intubation, all of which should increase patient comfort and allow a thorough endoscopic examination. Rex et al also
described a need for lower sedation medication dosages with the use of water-based methods [4]. Potential disadvantages of water-based methods include the increased overall procedural time, as highlighted by Cadoni et al [5]. On the other hand, the air/CO$_2$ insufflation (ACI) method is the most prevalent and has been associated with lower rates of perforation and post-procedural pain. The ACI method is also considered essential for procedures such as endoscopic mucosal dissection, wide-field endoscopic mucosal resection, and colorectal stent placement. The biggest challenge with this method is filling a gravity-dependent colon with gas, usually carbon dioxide [4].

Adenoma detection rate (ADR) is an important quality indicator during colonoscopy [6]. An increase in ADR has been strongly linked to a decrease in the incidence of colorectal cancer (CRC) and subsequent mortality [7]. Fuccio et al compared the WE, WI and ACI methods in a comparative meta-analysis and demonstrated the superiority of the WE method over both WI and ACI in terms of overall adenoma detection rate and right colon adenoma detection rate (RADR) [8]. Another network meta-analysis by Facciorusso et al supported the use of water techniques for improving overall ADR [9]. Critically, the authors of this study did not perform an analysis of the proximal adenoma detection rate (PADR).

Proximal colon adenomas, owing to their location and nature, have higher rates of being missed during colonoscopy [10-14]. Efforts are being made to increase PADR in order to decrease the overall interval incidence of CRC [15-17]. We performed a systematic review and meta-analysis of the available literature to compare the WE, WI and ACI techniques with a focus on the PADR obtained when each of these approaches were used.

**Patients and methods**

**Study definitions**

PADR is defined as the proportion of patients with at least 1 adenoma detected proximal to the splenic flexure. RADR is defined as the proportion of patients with at least 1 adenoma detected in the cecum and/or ascending colon. The ACI method is defined as insufflation of the colon using either air or CO$_2$, without the use of water.

**Search strategy**

We searched the following databases from inception through July 31$^{st}$, 2019, to generate a comprehensive and up-to-date list of articles for the purposes of this systematic review: PubMed/MEDLINE, Embase, Cochrane Register of Controlled Trials, Web of Science Core Collection, and CINAHL. Controlled subject terms and keyword synonyms for the concepts of colonoscopy, adenoma/polyp detection rate, and water/underwater method were developed for PubMed and translated to the vocabularies and syntax of the other databases. The search strategy was created and performed by (WL-S) and cross checked by another reviewer (MA). Pertinent articles were finalized by 2 reviewers (MA and SS). We adhered to the PRISMA guidelines for this systematic review. The detailed search strategy for PubMed is highlighted in Supplementary Table 1.

**Inclusion and exclusion criteria**

We restricted our systematic review to include only randomized controlled trials (RCT) and cohort studies. All other studies, including editorials, case reports, case series, and single-arm studies were excluded. Abstracts were also included in this review if they adhered to study design, i.e. RCT or cohort. Our search was not restricted to language or dates. If studies were found to contain duplicate data, the most recent available study was included.

**Data collection**

Baseline demographic data (age, sex), colonoscopy indication (screening/surveillance vs. diagnostic), and outcomes (PADR, RADR, and CIR) were extracted where applicable. Data extraction was performed by 2 individual reviewers (MA and SS) and cross-checked for any discrepancies.

**Primary and secondary outcomes**

The primary outcome of our analysis was PADR; secondary outcomes included RADR and CIR. We performed a comparative head-to-head meta-analysis of each technique for the WE, WI and ACI groups, where applicable. In addition, subgroup analysis was performed based on full articles and study design.

**Statistical analysis**

Data were extracted using Microsoft Excel (Microsoft, Redmond, Washington, United States). Risk ratio (RR) with 95% confidence interval (CI) were calculated for all pooled proportional outcomes. The DerSimonian-Laird method and a random-effects model were used as computing techniques and Open Meta Analyst (CEBM, University of Oxford, Oxford, United Kingdom) was used as the computing software for generating all outcomes. The fixed-effect model was used as a sensitivity tool. Heterogeneity was evaluated using the $I^2$ statistic between the studies, defined by Cochrane handbook for systematic reviews. Percentages of 25% ($I^2=25$), 50% ($I^2=50$), and 75% ($I^2=75$) were considered to represent low, moderate and high degrees of heterogeneity, respectively [18,19]. A P-value <0.05 was considered statistically significant for all outcomes between the 2 groups.
Bias assessment

Study quality was assessed using Cochrane risk-of-bias tools for RCTs and the Newcastle Ottawa score for cohort studies [20,21]. Publication bias was assessed using Egger’s regression analysis, and was displayed using funnel plots generated using Review Manager V5.3 (The Cochrane Collaboration, Oxford, United Kingdom), where applicable.

Evidence rating

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the overall quality of evidence (high, moderate, low, very low) and provided summary of funding (SoF) Tables. We utilized GRADEpro GDT software (Evidence Prime Inc., Hamilton, Ontario, Canada) to generate the SoF Tables [22].

Results

A total of 12 studies with 17 arms were included in the final analysis for this systematic review and meta-analysis (Fig. 1) [23-34]. Of these, all were RCTs except one cohort study [32]. Nine of these studies were published as full manuscripts and 2 were published as abstracts. Two studies by Cadoni et al included data from the same RCT and hence we only included data once while comparing outcomes [26,27].

The risk-of-bias assessment is shown in Supplementary Table 2. All RCTs had high performance bias, as it was impossible to blind the endoscopist performing the procedure. We were unable to perform the bias assessment on the cohort study as it was an abstract. No significant publication bias was observed based on the funnel plot obtained (Supplementary Fig. 1) or Egger’s regression test (P=0.34).

Study details and demographics of patients are summarized in Supplementary Table 3 and Table 1. Of all the studies included, 11 directly compared ACI to WE [23-34] and 4 directly compared ACI to WI [26,28,30,34]. The total number of patients included in these 11 studies was 5660 (2260 ACI, 2281 WE, 1119 WI). No statistically significant difference was observed in terms of age range (54.8-63.6, 55.7-63.1, and 54.3-61) or the proportion male sex (65.3%, 64.9%, and 55.3%) across the 3 groups for ACI, WE and WI, respectively. The primary and secondary outcomes for individual studies are summarized in Table 2.

### Table 1 Demographics and characteristics of patients included in the study

| Study          | Mean/Median Age, n | Male, n (%) | Indication for colonoscopy, n (%) | Study completion, n (%) |
|----------------|--------------------|-------------|-----------------------------------|------------------------|
|                | Control            | Intervention| Control                           | Intervention            | Control | Intervention|
| Manuscripts    |                    |             |                                   |                        |         |             |
| Leung et al [24] | 62.1               | 63.1        | 88 (97.8%)                        | 91 (98.9%)             | Sc/Su: 81 (90.0%) | D/O: 9 (10.0%) | 90 (100.0%) | 92 (100.0%) |
| Ramirez et al [31] | 59.3               | 60          | 184 (96.3%)                       | 171 (96.6%)            | Sc/Su: 191 (100.0%) | D/O: 0 (0%) | 191 (100.0%) | 177 (100.0%) |
| Hsieh et al [34] | 56.5               | 55.6        | 60 (66.7%)                        | 108 (60.0%)            | Sc/Su: 35 (38.9%) | D/O: 55 (61.1%) | 90 (100.0%) | 180 (100.0%) |
| Cadoni et al [29] | 60                 | 58          | 204 (61.1%)                       | 201 (59.5%)            | Sc/Su: 140 (41.9%) | D/O: 194 (58.1%) | 334 (82.3%) | 338 (82.4%) |
| Cadoni et al [26,27] | 59                 | 59          | 239 (59.6%)                       | 465 (58.2%)            | Sc/Su: 97 (24.2%) | D/O: 304 (75.8%) | 401 (100.0%) | 799 (100.0%) |
| Cadoni et al [28] | 60.9               | 61.2        | 225 (55.1%)                       | 447 (54.8%)            | Sc/Su: 408 (100.0%) | D/O: 0 (0%) | 408 (100.0%) | 816 (100.0%) |
| Hsieh et al [30] | 54.8               | 55.8        | 105 (48.4%)                       | 231 (53.2%)            | Sc/Su: NR | D/O: NR | 217 (100.0%) | 434 (100.0%) |
| Azevedo et al [25] | 63.6               | 61.6        | 40 (56.3%)                        | 41 (58.6%)             | Sc/Su: 44 (62.0%) | D/O: 27 (38.0%) | 71 (87.7%) | 70 (85.4%) |
| Leung et al [23] | 60.8               | 60.5        | 145 (91.2%)                       | 138 (85.7%)            | Sc/Su: 159 (100.0%) | D/O: NR | 159 (100.0%) | 161 (100.0%) |
| Abstracts      |                    |             |                                   |                        | Sc/Su: NR | D/O: NR |            |            |
| Boroff et al [32] | NR                 | NR          | NR                                | NR | Sc/Su: 157 (100.0%) | D/O: 0 (0%) | 157 (100.0%) | 189 (100.0%) |
| Chu et al [33]  | 58.2               | 57.9        | 30 (50.0%)                        | 29 (48.3%)             | Sc/Su: 56 (93.3%) | D/O: 4 (6.7%) | 60 (100.0%) | 60 (100.0%) |

D/O, diagnostic/others; n, no. of patients; NR, not reported; Sc/Su, screening/surveillance
How to increase proximal adenoma detection rate

Table 2 Primary and secondary outcomes for all studies

| Study          | PADR, n (%) | RADR, n (%) | CIR, n (%) |
|----------------|-------------|-------------|------------|
|                | Control     | Intervention | Control     | Intervention | Control     | Intervention |
| Manuscripts    |             |             |             |             |             |             |
| Leung et al [24] | ACI: 15 (16.7%) | WE: 27 (29.3%) | NR | NR | ACI: 81 (90.0%) | WE: 91 (99.0%) |
| Ramirez et al [31] | ACI: 66 (34.6%) | WE: 81 (45.8%) | NR | NR | ACI: 191 (100.0%) | WE: 163 (92.1%) |
| Hsieh et al [34] | ACI: 16 (17.8%) | WE: 29 (32.2%) | ACI: 10 (11.1%) | WE: 24 (26.7%) | ACI: 71 (78.9%) | WE: 82 (91.1%) |
| WI: 25 (27.8%) | WI: 13 (14.4%) | WI: 83 (92.2%) | | | | |
| Cadoni et al [29] | ACI: 16 (4.8%) | WE: 34 (10.1%) | NR | NR | ACI: 330 (98.8%) | WE: 326 (96.4%) |
| Cadoni et al [26, 27] | ACI: 51 (21.3%) | WE: 60 (25.9%) | ACI: 48 (12.0%) | WE: 59 (14.9%) | ACI: 234 (97.9%) | WE: 228 (98.3%) |
| WI: 25 (20.6%) | WI: 49 (12.1%) | WI: 228 (97.8%) | | | | |
| Cadoni et al [28] | NR | NR | ACI: 69 (16.9%) | WE: 98 (24.0%) | ACI: 399 (97.8%) | WE: 402 (98.5%) |
| WI: 78 (19.1%) | WI: 228 (97.8%) | WI: 400 (98.0%) | | | | |
| Hsieh et al [30] | ACI: 44 (20.3%) | WE: 64 (29.5%) | ACI: 33 (15.3%) | WE: 47 (21.7%) | ACI: 197 (90.8%) | WE: 208 (95.9%) |
| WI: 66 (30.4%) | WI: 38 (17.5%) | WI: 191 (88.0%) | | | | |
| Azevedo et al [25] | NR | NR | ACI: 4 (5.6%) | WE: 6 (8.6%) | NR | NR |
| Leung et al [23] | ACI: 83 (52.2%) | WE: 86 (53.4%) | NR | NR | ACI: 156 (98.1%) | WE: 161 (100.0%) |
| Abstracts       |             |             |             |             |             |             |
| Boroff et al [32] | ACI: 51 (32.5%) | WE: 64 (33.9%) | NR | NR | NR | NR |
| Chu et al [33] | NR | NR | ACI: 5 (8.3%) | WE: 7 (11.7%) | ACI: 56 (93.3%) | WE: 59 (98.3%) |

ACI, air/CO2 colonoscopy; CIR, cecal intubation rate; n, no. of studies; NR, not reported; PADR, proximal adenoma detection rate; RADR, right adenoma detection rate; WE, water exchange colonoscopy; WI, water immersion colonoscopy

460 records identified through database searching
63 in PubMed
121 in Cochrane Library
169 in Embase
79 in Web of Science
28 in CINAHL

192 duplicate records excluded

268 records after duplicates removed were screened

220 records excluded on title and abstract screening

48 articles were assessed for eligibility

37 studies were excluded on further screening because of irrelevant study design, different interventions and/or irrelevant outcomes.

12 studies (17 arms) with allocation of patients to either Air/CO2 insufflation group or Water exchange / Water immersion group included in quantitative synthesis

Figure 1 Flow diagram representing the selection of studies
### Table 3 Summary of findings

Water exchange technique compared to air/CO$_2$ insufflation for colonoscopy

| Outcomes | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|----------|------------------------------------------|--------------------------|-------------------------------|----------------------------------|
| PADR assessed with: colonoscopy, biopsy, histology | Risk with air/CO$_2$ insufflation: 220 per 1000 (Risk with water exchange technique: 287 per 1000) | RR 1.30 (1.05 to 1.62) | 2627 (7 RCTs) | ⊕⊕⊕ MODERATE* |
| RADR assessed with: colonoscopy, biopsy, histology | Risk with air/CO$_2$ insufflation: 138 per 1000 (Risk with water exchange technique: 198 per 1000) | RR 1.43 (1.19 to 1.71) | 2367 (5 RCTs) | ⊕⊕⊕ MODERATE* |
| CIR assessed with: colonoscopy | Risk with air/CO$_2$ insufflation: 953 per 1000 (Risk with water exchange technique: 972 per 1000) | RR 1.020 (0.991 to 1.051) | 2891 (8 RCTs) | ⊕⊕⊕ MODERATE** |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence:
- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

- **a.** Participants and endoscopist were not blinded during colonoscopy for practical reasons.
- **b.** Studies reported varying intubation rate.

#### Figure 2

Forest plot comparing PADR in (A) WE versus ACI group (B) WI versus ACI group

C.I., confidence interval; ACI, air/CO$_2$ insufflation colonoscopy; Trt, WE group; Ctrl, ACI group; PADR, proximal adenoma detection rate; WE, water exchange colonoscopy; WI, water immersion colonoscopy.
PADR

Overall, 8 studies reported PADR [23,24,27,29-32,34]. The 8 arms comparing WE to ACI revealed a higher PADR for the WE group (WE: 29.7%, 95%CI 21.8-41.9% vs. ACI: 23.2%, 95%CI 14.1-33.8%; RR 1.30, 95%CI 1.11-1.53; P=0.001; I²=43.5%) (Fig. 2A). Only 3 arms compared WI to ACI and found no difference in PADR between them (WI: 26.0%, 95%CI 19.4-33.3% vs. ACI: 20.3%, 95%CI 17.2-23.9%; RR 1.28, 95%CI 0.93-1.76; P=0.13; I²=48.1%) (Fig. 2B).

![Figure 3](https://example.com/fig3.png)

**Figure 3** Forest plot comparing RADR in (A) WE vs. ACI group (B) WI vs. ACI group. C.I., confidence interval; ACI, air/CO₂ insufflation colonoscopy; Trt, WE group; Ctrl, ACI group; RADR, right adenoma detection rate; WE, water exchange colonoscopy; WI, water immersion colonoscopy

![Figure 4](https://example.com/fig4.png)

**Figure 4** Forest plot comparing CIR in (A) WE vs. ACI group (B) WI vs. ACI group. C.I., confidence interval; ACI, air/CO₂ insufflation colonoscopy; Trt, WE group; Ctrl, ACI group; CIR, cecal intubation rate; WE, water exchange colonoscopy; WI, water immersion colonoscopy

Annals of Gastroenterology 33
Overall 5 studies reported RADR [25,28,30,31,34]. RADR was significantly greater in the WE group compared to the ACI group, with a direct comparison in 5 arms (WE: 19.8%, 95%CI 14.6-25.4% vs. ACI: 13.8%, 95%CI 10.4-16.9%; RR 1.43, 95%CI 1.19-1.71; P≤0.001; I²=0%) (Fig. 3A). Four arms compared the WI to the ACI group and found no difference in RADR (WI: 15.9%, 95%CI 12.4-19.9% vs. ACI: 14.3%, 95%CI 11.7-17.3%; RR 1.11, 95%CI 0.91-1.35; P=0.29; I²=0%) (Fig. 3B).

No significant difference was observed in CIR for either comparison: i.e. WE vs. ACI (97.0% vs. 95.3%, RR 1.02, 95%CI 0.99-1.05; P=0.18; I²=77.7%) (Fig. 4A) and WI vs. ACI (92.2% vs. 93.8%, RR 0.99, 95%CI 0.94-1.05; P=0.76; I²=83.3%) (Fig. 4B).

A subgroup analysis of only published RCTs showed higher PADR (28.8% vs. 22.8%, RR 1.30, 95%CI 1.05-1.62; P=0.02; I²=51.5%) and RADR (19.8% vs. 13.8%, RR 1.43, 95%CI 1.19-1.71; P≤0.001; I²=0%) in the WE group compared to the ACI group. PADR for screening colonoscopies was available in 3 studies and a higher detection rate was found for the WE group; however, the results were not statistically significant (41.9% vs. 33.5%, RR 1.31, 95%CI 0.93-1.85; P=0.13; I²=70.9%).

### Evidence rating

Using the GRADE approach, the certainty of evidence was moderate for PADR and RADR assessed for WE vs. ACI colonoscopy (Table 3). The certainty of evidence was low and moderate for PADR and RADR, respectively, when the WI and ACI techniques were compared (Table 4).

### Discussion

The results of our systematic review and meta-analysis demonstrate a greater PADR and RADR for the WE compared to the ACI method. This was also consistent with our subgroup analysis of RCTs. No difference in detection
rates was observed when the WI group was compared with the ACI group.

The exact mechanism through which WE improves colonoscopy outcome metrics, such as ADR, RADR and PADR, is not fully understood. One possible theory points to the greater cleanliness throughout the colon achieved through simultaneous water infusion and suction in the WE method, as shown by Fuccio et al [8]. Another possible mechanism is the magnifying effect of water itself on the endoscope optics during the insertion phase, leading to higher detection rates [34]. Lastly, a thorough examination is possible, as the WE technique eliminates the need for constant washing and suctioning and hence reduces the incidence of luminal collapse [35]. A combination of the aforementioned factors may increase the yield of colonoscopy outcome metrics and decrease the incidence of interval CRC.

Proximal lesions can be challenging to detect, because of their location and subtle appearance. Sessile serrated adenomas/polyps (SSA/Ps), a subset of these lesions, are particularly important, as they may account for ~20% of all CRC cases [36]. Yang et al previously showed that 61.2% of SSA/Ps were found in the proximal colon [37]. This further necessitates the improvement of techniques to increase detection of these proximal lesions. Only one study directly evaluated SSA/Ps, showing a significantly greater detection rate of these lesions using the WE method compared to the ACI method (23.6% vs. 11.3%, P<0.01) [23]. Our meta-analysis is important, as we pooled data from all available studies regarding proximal adenomas and our results demonstrate the superiority of the WE method in detecting these lesions; this, in turn, should increase the detection rate for SSA/Ps.

The current meta-analysis has some limitations. Not all studies reported both PADR and RADR for each technique; however, a sufficient number of patients were analyzed to generate a pooled outcome for each metric. Our results for PADR showed some degree of heterogeneity and hence the results should be interpreted with caution. The heterogeneity can be explained by a combination of endoscopist skill, the inclusion of cohort study design, the indications for colonoscopy, procedural technicalities such as method of sedation, use of adjunctive modalities such as distal attachments or chromoendoscopy, etc. To compensate for this, we tried to limit our search criteria to exclude studies that used additional adjunctive modalities. The subgroup analysis for only RCTs also showed consistent results for both PADR and RADR using the WE method compared to the ACI method. The studies included were reported from limited institutions with expert endoscopists and the results may not be generalizable to a general population. Lastly, the impracticality of blinding the endoscopist and patient during a study does bring performance and detection bias into play. The limitations are partly attenuated by the combined statistical power of large number of studies with diverse study populations. All studies except one were RCTs and we used strict inclusion and exclusion criteria for screening studies.

In conclusion, the use of WE during colonoscopy showed significantly better PADR and RADR compared to the ACI method. Given the importance of SSA/Ps, future studies should be conducted to directly assess the use of the WE method to evaluate the detection rate of these lesions.

### Summary Box

**What is already known:**
- The water exchange technique has been found to have significantly better detection rates for polyps and adenomas
- Previous meta-analyses have demonstrated the efficacy of water exchange techniques in improving overall adenoma detection rate (ADR), right ADR (RADR), and polyp detection rate

**What the new findings are:**
- Our meta-analysis evaluated proximal adenoma detection rate (PADR), which is another outcome metric
- The water exchange technique showed significantly better PADR and RADR compared to standard (air/CO₂) insufflation colonoscopy
- Given the efficacy of water exchange techniques, clinicians should be encouraged to utilize them to further improve their colonoscopy outcome metrics

### References

1. Leung FW, Harker JO, Jackson G, et al. A proof-of-principle, prospective, randomized, controlled trial demonstrating improved outcomes in scheduled unsedated colonoscopy by the water method. *Gastrointest Endosc* 2010; 72:693-700.
2. Leung CW, Kaltenbach T, Soetikno R, Wu KK, Leung FW, Friedland S. Water immersion versus standard colonoscopy insertion technique: randomized trial shows promise for minimal sedation. *Endoscopy* 2010; 42:557-563.
3. Cadoni S, Ishaq S. How to perform water-aided colonoscopy, with differences between water immersion and immersion water exchange: a teaching video demonstration. *VideoGIE* 2018; 3:169-170.
4. Rex DK. Water filling and carbon dioxide insufflation: tools for every colonoscopist. *Clin Gastroenterol Hepatol* 2015; 13:1981-1983.
5. Cadoni S, Hassan C, Frazzoni L, Ishaq S, Leung FW. Impact of water exchange colonoscopy on endoscopy room efficiency: a systematic review and meta-analysis. *Gastrointest Endosc* 2019; 89:159-167.
6. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc* 2015; 81:53-51.
7. Kaminowski MF, Wieszczyn P, Rupinski M, et al. Increased rate of adenoma detection associates with reduced risk of colorectal cancer and death. *Gastroenterology* 2017; 153:98-105.
8. Fuccio L, Frazzoni L, Hassan C, et al. Water exchange colonoscopy increases adenoma detection rate: a systematic review with network meta-analysis of randomized controlled studies. *Gastrointest Endosc* 2018; 88:589-597.
9. Facciorusso A, Triantaphyllou K, Murad MH, et al. Compared abilities of endoscopic techniques to increase colon adenoma detection rates: a network meta-analysis. *Clin Gastroenterol Hepatol* 2019; 17:2439-2454.
10. Zhao S, Wang S, Pan P, et al. Magnitude, risk factors, and factors
associated with adenoma miss rate of tandem colonoscopy: a systematic review and meta-analysis. Gastroenterology 2019;156:1661-1674.

11. Lee J, Park SW, Kim YS, et al. Risk factors of missed colorectal lesions after colonoscopy. Medicine (Baltimore) 2017;96:e7468.

12. Zimmermann-Faerdrich K, Sehner S, Rex DK, et al. Right-sided location not associated with missed colorectal adenomas in an individual-level reanalysis of tandem colonoscopy studies. Gastroenterology 2019;157:660-671.

13. Chokshi RV, Hovis CE, Hollander T, Early DS, Wang JS. Prevalence of missed adenomas in patients with inadequate bowel preparation on screening colonoscopy. Gastrointest Endosc 2012;75:1197-1203.

14. Ahn SB, Han DS, Bae JH, Byun TJ, Kim JP, Eun CS. The miss rate for colorectal adenoma determined by quality-adjusted, back-to-back colonoscopies. Gut Liver 2012;6:64-70.

15. Klare P, Philipsen H, Haller B, et al. Longer observation time increases adenoma detection in the proximal colon - a prospective study. Endosc Int Open 2017;5:E1289-E1298.

16. Desai M, Sanchez-Yague A, Choudhary A, et al. Impact of cap-assisted colonoscopy on detection of proximal colon adenomas: systematic review and meta-analysis. Gastrointest Endosc 2017;86:274-281.

17. Aziz M, Desai M, Hassan S, et al. Improving serrated adenoma detection rate in the colon by electronic chromoendoscopy and distal attachment: systematic review and meta-analysis. Gastrointest Endosc 2019;90:721-731.

18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

19. Shuster J. Review: Cochrane handbook for systematic reviews for interventions, Version 5.1.0, published 3/2011. Higgins JPT, Green S (editors).

20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring risk of bias in randomised trials. BMJ 2011;343:d5928.

21. Deeks JJ, Dinnes J, D’Amico R, et al; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:i-x.

22. Zhang Y, Akl EA, Schünemann HJ. Using systematic reviews in guideline development: the GRADE approach. Res Synth Methods 2019;10:312-329.

23. Leung JW, Yen AW, Ia H, et al. A prospective RCT comparing combined chromoendoscopy with water exchange (CWE) vs water exchange (WE) vs air insufflation (AI) in adenoma detection in screening colonoscopy. United European Gastroenterol J 2019;7:477-487.

24. Leung FW, Leung JW, Siao-Salera RM, Mann SK. The water method significantly enhances proximal diminutive adenoma detection rate in unsedated patients. J Inter J Gastroenterol 2011;1:8-13.

25. Azevedo R, Leitão C, Pinto J, et al. Can Water Exchange Improve Patient Tolerance in Unsedated Colonoscopy A Prospective Comparative Study. GE Port J Gastroenterol 2018;25:166-174.

26. Cadoni S, Falt P, Sanna S, et al. Impact of colonoscopy insertion techniques on adenoma detection. Dig Dis Sci 2016;61:2068-2075.

27. Cadoni S, Falt P, Sanna S, et al. Insertion water exchange increases right colon adenoma and hyperplastic polyp detection rates during withdrawal. Dig Liver Dis 2016;48:638-643.

28. Cadoni S, Falt P, Rondonotti E, et al. Water exchange for screening colonoscopy increases adenoma detection rate: a multicenter, double-blinded, randomized controlled trial. Endoscopy 2017;49:456-467.

29. Cadoni S, Gallittu P, Sanna S, et al. A two-center randomized controlled trial of water-aided colonoscopy versus air insufflation colonoscopy. Endoscopy 2014;46:212-218.

30. Hsieh YH, Tseng CW, Hu CT, Koo M, Leung FW. Prospective multicenter randomized controlled trial comparing adenoma detection rate in colonoscopy using water exchange, water immersion, and air insufflation. Gastrointest Endosc 2017;86:192-201.

31. Ramirez FC, Leung FW. A head-to-head comparison of the water vs. air method in patients undergoing screening colonoscopy. J Inter J Gastroenterol 2011;1:130-135.

32. Boroff E, Ruff KC, Ramirez FC. Sa1430: Outcomes of the water assisted colonoscopy on detection of proximal colon adenomas: a multicenter randomized controlled trial. Endoscopy 2017;49:467-470.

33. Ramirez FC, Leung FW. A head-to-head comparison of the water vs. air method in patients undergoing screening colonoscopy. J Inter J Gastroenterol 2011;1:130-135.

34. Hsieh YH, Koo M, Leung FW. A prospective randomized, controlled trial comparing air insufflation, water immersion, and air insufflation colonoscopy. Gastrointest Endosc 2015;81:AB212.

35. Chu VW, Li EH, Cheung ML, et al. Sa1439: Water exchange colonoscopy reduced sedation requirement without compromising success of cecal intubation in patients accepting the option of on demand sedation in Chinese patients in Hong Kong. Gastrointest Endosc 2015;81:AB216.

36. Hsieh YH, Koo M, Leung FW. A patient-blinded randomized, controlled trial comparing air insufflation, water immersion, and water exchange during minimally sedated colonoscopy. Am J Gastroenterol 2014;109:1390-1400.

37. Yen AW. Insertion water exchange minimizes endoscopist multitasking during withdrawal inspection-a plausible explanation for enhanced polyp detection in the right colon. J Inter Gastroenterol 2015;5:3.

38. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology 2010;138:2088-2100.

39. Yang JP, Tang SJ, Lash RH, Wu R, Yang Q. Anatomic distribution of sessile serrated adenoma/polyp with and without cytologic dysplasia. Arch Pathol Lab Med 2015;139:388-393.
Supplementary material

Supplementary Table 1 PubMed search strategy

| Search | Query | Items found |
|--------|-------|-------------|
| #1     | (Underwater* OR water OR "Water" [Mesh: NoExp]) | 939742 |
| #2     | ("Colonoscopy" [Mesh] OR colonoscop* OR coloscop*) | 42494 |
| #3     | ("Adenoma" [Mesh] OR "Polyps" [Mesh] OR adenoma* OR polyp OR polyps) | 172518 |
| #4     | (Detect* OR miss] AND [rate or rates]) | 291521 |
| #5     | #3 AND #4 | 4737 |
| #6     | #1 AND #2 | 642 |
| #7     | #5 AND #6 | 82 |
| #8     | #7 NOT ("case reports" [Publication Type] OR "guideline" [Publication Type] OR "introductory journal article" [Publication Type] OR "review" [Publication Type]) | 63 |

Supplementary Table 2 Risk of bias in the included randomized controlled trials (RCTs)

| Study            | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|------------------|-------------------------------------------|-----------------------------------------|--------------------------------------------------------|---------------------------------------------|---------------------------------------|-------------------------------------|
| Leung et al [24] | Unclear                                   | Unclear                                 | High                                                   | Unclear                                     | Low                                   | Low                                 |
| Ramirez et al [31] | High                                      | Unclear                                 | High                                                   | Low                                         | Low                                   | Low                                 |
| Hsieh et al [34] | Low                                       | Unclear                                 | High                                                   | High                                        | Low                                   | Low                                 |
| Cadoni et al [29] | Low                                       | Unclear                                 | High                                                   | Low                                         | Low                                   | Low                                 |
| Cadoni et al [26, 27] | Unclear                                  | Unclear                                 | High                                                   | Low                                         | Low                                   | Low                                 |
| Cadoni et al [28] | Low                                       | Low                                     | High                                                   | Low                                         | Low                                   | Low                                 |
| Hsieh et al [30] | Unclear                                   | Low                                     | High                                                   | Unclear                                     | Low                                   | Low                                 |
| Azevedo et al [25] | Low                                       | Low                                     | High                                                   | Low                                         | Low                                   | Low                                 |
| Leung et al [23] | Low                                       | Low                                     | High                                                   | Low                                         | Low                                   | Low                                 |

*Cadoni 2, 3 included data from the same RCT and are hence included as one here

Supplementary Table 3 Study details

| S. No | Study-year | Type of Study | Year | Techniques compared | Total (n) | Control group (n) | Intervention group (n) |
|-------|------------|---------------|------|---------------------|-----------|-------------------|-----------------------|
| Manuscripts |          |               |      |                     |           |                   |                       |
| 1.    | Leung et al [24] | RCT  | 2011 | WE vs. ACI        | 182       | 90                | 92                    |
| 2.    | Ramirez et al [31] | RCT  | 2011 | WE vs. ACI        | 368       | 191               | 177                   |
| 3.    | Hsieh et al [34] | RCT  | 2014 | WE vs. WI vs. ACI  | 270       | 90                | 180 (WE: 90, WI: 90)  |
| 4.    | Cadoni et al [29] | RCT  | 2014 | WE vs. ACI        | 816       | 406               | 410                   |
| 5.    | Cadoni et al [26,27] | RCT  | 2016 | WE vs. WI vs. ACI  | 1200      | 401               | 799 (WE: 395, WI: 404) |
| 6.    | Cadoni et al [28] | RCT  | 2017 | WE vs. WI vs. ACI  | 1224      | 408               | 816 (WE: 408, WI: 408) |
| 7.    | Hsieh et al [30] | RCT  | 2017 | WE vs. WI vs. ACI  | 651       | 217               | 434 (WE: 217, WI: 217) |
| 8.    | Azevedo et al [25] | RCT  | 2018 | WE vs. ACI        | 163       | 81                | 82                    |
| 9.    | Leung et al [23] | RCT  | 2019 | WE vs. ACI        | 320       | 159               | 161                   |

Abstracts

| S. No | Study-year | Type of Study | Year | Techniques compared | Total (n) | Control group (n) | Intervention group (n) |
|-------|------------|---------------|------|---------------------|-----------|-------------------|-----------------------|
| 1.    | Boroff et al [32] | Cohort  | 2015 | WE vs. ACI        | 346       | 157               | 189                   |
| 2.    | Chu et al [33] | RCT  | 2015 | WE vs. ACI        | 120       | 60                | 60                    |

*Cadoni (2, 3) included data from the same RCT and hence included as one here

CI, air/CO₂ insufflation colonoscopy; n, no. of patients; RCT, randomized controlled trials; WE, water exchange colonoscopy; WI, water immersion colonoscopy
Supplementary Figure 1 Funnel plot demonstrating no visible asymmetry (signifying no publication bias), based on cecal intubation rate

RR, risk ratio; SE, standard error