Accepted Manuscript online: 2022-07-11 Article published online: 2022-10-17

Second exam of right colon improves adenoma detection rate: Systematic review and meta-analysis of randomized controlled trials

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Supplementary material is available under https://doi.org/10.1055/a-1896-4499

submitted 27.12.2021
accepted after revision 8.7.2022
published online 11.7.2022

Bibliography
Endosc Int Open 2022; 10: E1391–E1398
DOI 10.1055/a-1896-4499
ISSN 2364-3722

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ABSTRACT

Background and study aims A second examination of the right colon, either as a second forward view (SFV) or as retroflexion (RF) in the cecum, can increase adenoma detection rate (ADR) in the right colon. In this meta-analysis, we have evaluated the role of a second examination of the right colon in improving ADR.

Methods We reviewed several databases to identify randomized controlled trials that compared right colon SFV with no SFV, and RCTs that compared SFV with RF in the right colon, and reported data on ADR. Our outcomes of interest were ADR and polyp detection rate (PDR) with SFV vs no SFV, right colon and total withdrawal times, and additional ADR and PDR with SFV vs RF. For categorical variables, we calculated pooled risk ratios (RRs) with 95% confidence intervals (CIs); for continuous variables, we calculated standardized mean difference (SMD) with 95% CI. Data were analyzed using random effects model.

Results We included six studies with 3901 patients. Comparing SFV with no SFV, right colon ADR and PDR were significantly higher in the SFV group: ADR (RR [95% CI] 1.39 [1.22,1.58]) and PDR (RR [95% CI] 1.47 [1.30, 1.65]). We found no significant difference in right colon withdrawal time (SMD [95% CI] 1.54 [−0.20,3.28]) or total withdrawal time (SMD (95% CI) 0.37 [−0.39,1.13]) with and without SFV. We found no significant difference in additional ADR between SFV and RF.

Conclusions SFV of the right colon significantly increases right-sided and overall ADR.

Introduction

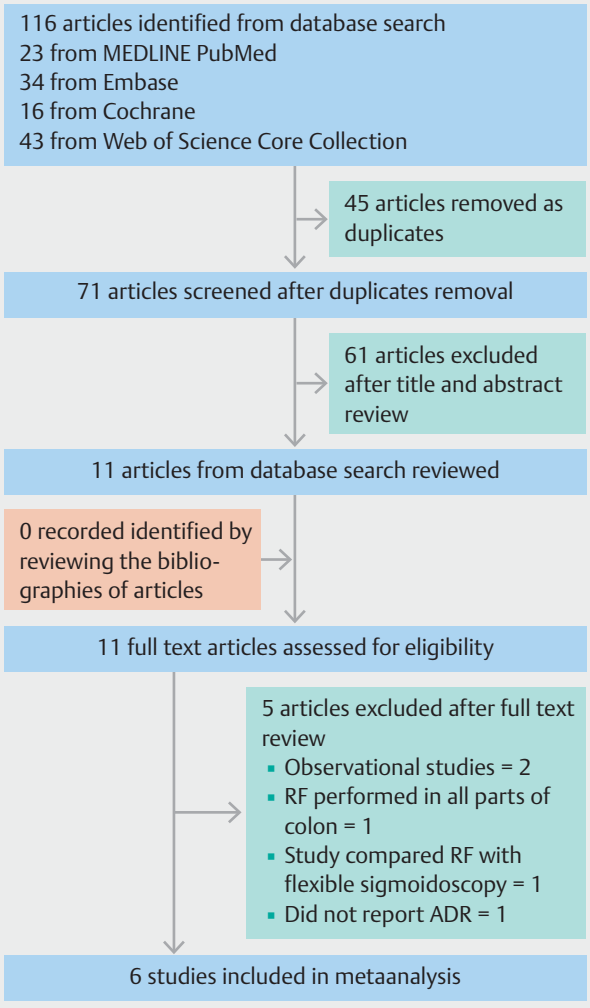
Colonoscopy is considered the gold standard for colon cancer screening. Colonoscopic detection and resection of polyps reduces colon cancer incidence and mortality [1,2]. Missing polyps during colonoscopy is a substantial clinical problem that may decrease the efficacy of colonoscopy in the prevention of colon cancer [3,4]. One meta-analysis including 43 studies and over 15,000 tandem colonoscopies found that the adenoma miss rate (AMR) was 26% [5]. Some studies have found colonoscopy to be less effective in the prevention of proximal than distal colon cancer [2,6,7]. This may be partly explained by the morphology of right colon polyps, which are more likely to be flat and more easily missed during colonoscopy [8]. Cancers in the right colon are often diagnosed at an advanced stage and carry a worse prognosis than left-sided cancers, due possibly to different mechanisms of carcinogenesis [9,10].

The adenoma detection rate (ADR) at colonoscopy is inversely associated with the risk of interval colorectal cancer [11]. A second examination of the right colon either with a second forward view (SFV) or retroflexion (RF) in the cecum increases ADR and the polyp detection rate (PDR) of right-sided polyps [12–14]. A previous meta-analysis [15] that included both observational studies and randomized controlled trials (RCTs) found that SFV and RF of the right colon independently increased ADR. Since then, additional RCTs have compared SFV with no SFV, and SFV with RF, in the right colon and have reported data on right colon ADR [16–19]. In order to examine this further, we have conducted an updated systematic review and meta-analysis confined only to RCTs to evaluate the role of a second examination of the right colon in improving ADR.

Methods

Data sources and search strategy

We followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). The PRISMA checklist is provided in **Supplementary Fig. 1**. An experienced medical librarian (W. L-S.) performed a comprehensive search of MEDLINE (PubMed platform), Embase (Embase.com, Elsevier), Web of Science Core Collection (Clarivate) and the Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) from inception to January 21, 2021 and subsequently updated the results on August 2, 2021. There was no restriction of publication language in conducting the search. The search included truncation-expanded keywords and database-specific subject terms for SFV of the right colon, right colon RF, and ADR. We have provided full search strategies from all databases in **Supplementary Fig. 2**. Two authors (F.K. and S.S.) independently reviewed the titles and abstracts of the retrieved articles and excluded those that did not provide data on our outcomes of interest. Full texts of remaining articles were reviewed. We also reviewed the bibliographies of these articles to identify any additional relevant studies. The screening results are illustrated in the form of a PRISMA flowchart in ▶ **Fig. 1**.



▶ **Fig. 1** PRISMA flowchart.

Inclusion and exclusion criteria

Two authors (F.K. and M.A.K.) independently searched for original studies based on pre-defined inclusion criteria, which are detailed below. We included only RCTs that compared SFV of the right colon or proximal colon with no SFV, and RCTs that compared SFV with RF in the right colon, and reported data on ADR. We excluded observational studies and review articles. We also excluded studies in which RF or SFV was performed in the distal or left colon. All citations were downloaded into Endnote X9 (Clarivate, Philadelphia, Pennsylvania, United States), a bibliographic database manager. Duplicate citations were removed by successive field matching algorithms with manual inspection.

Data extraction

Two authors (F.K. and M.A.K.) independently assessed the eligibility of included studies and collected data using data extraction forms designed for this study. Any disagreement between individual authors was resolved by a repeat review of data and

discussion with a third reviewer (C.W.H.). Extracted data included year of publication, patient demographics, inclusion criteria, exclusion criteria, ADR, PDR, right colon withdrawal time, and total withdrawal time.

Risk of bias assessment

We used the Cochrane tool for assessing risk of bias for RCTs to assess the quality of included studies. The Cochrane tool assesses the presence of selection bias by evaluating the methods of randomization and allocation concealment; performance and detection biases by checking for blinding of personnel and outcome assessment, respectively; and attrition and reporting bias by evaluating for incomplete and selective reporting of data, respectively. Two authors (Z.A. and U.F.) independently performed risk of bias assessment and any disagreement was discussed with a third reviewer (C.W.H.). The risk of bias assessment of RCTs is summarized in **Supplementary Table 1**.

Data synthesis and statistical analysis

Our primary outcome of interest was right colon ADR with SFV vs no SFV. Secondary outcomes of interest were right colon advanced ADR, PDR with SFV vs no SFV, overall ADR with SFV vs no SFV, right colon withdrawal time, total withdrawal time, difference in time spent in SFV vs RF in the right colon, additional ADR on SFV vs RF, and additional PDR on SFV vs RF. In all studies except one [20], the proximal or right colon was defined as being from the cecum to the hepatic flexure. The exception was a study by Guo et al [20], which defined the proximal colon as extending from the cecum to the splenic flexure. We therefore performed a sensitivity analysis by excluding that study. We calculated pooled risk ratios (RR) with 95 % confidence intervals (CI) to compare all outcomes, except withdrawal times, between groups. For the withdrawal times, we calculated standardized mean differences (SMD) with 95 % CI. We used Review Manager (RevMan, version 5.4 for Windows; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark, 2014) and comprehensive meta-analysis (CMA) software for statistical analyses. We used a random effects model to analyze the data. We assessed heterogeneity using the I^2 statistic. $P<0.1$ for Cochran Q test or $I^2>50\%$ indicated significant heterogeneity. We did not assess for publication bias as the total number of studies that we included was less than 10.

Assessment of quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess the quality of evidence. For systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. It classifies the quality of evidence as high, moderate, low or very low. For RCTs, the quality of evidence starts with high confidence; for observational studies, it starts with low confidence. It is further rated based on methodological quality (risk of bias), directness of evidence, inconsistency, precision of effect estimates, and publication bias. Details of quality of evidence for the outcomes based on GRADE are summarized in **Supplementary Table 2**.

Results

The search strategy produced 116 articles, 45 of which were removed as duplicates (▶ **Fig. 1**). From the remaining 71 articles, 60 were removed after title and abstract review. No additional relevant articles were identified from review of bibliographies. Full texts of 11 articles were reviewed. In one study, RF was performed in all parts of the colon rather than the cecum only; it was therefore excluded. Two studies were excluded since they were observational [21, 22]. One RCT reported data on AMR rather than ADR and was excluded [23]. One study that compared RF with flexible sigmoidoscopy was excluded [24]. Six studies [14, 16–20] with 3901 patients were included in the final analysis. Four studies [16–18, 20] with 2403 patients compared SFV with no SFV. Two studies [14, 19] with 1498 patients compared RF with SFV. The characteristics of included studies are summarized in ▶ **Table 1**.

Right colon ADR with SFV vs no SFV

Five studies with 3253 patients were included in this analysis. Pooled ADRs in the SFV and no SFV groups were 26 % and 18 %, respectively; RR (95 % CI) 1.39 (1.22,1.58), $I^2 = 0\%$ (▶ **Fig. 2**). On sensitivity analysis with exclusion of the study that defined the proximal colon as extending from the cecum to the splenic flexure [20], the result was consistent; RR (95 % CI) 1.38 (1.20,1.60), $I^2 = 0\%$. Quality of evidence on GRADE framework was high (**Supplementary Table 2**). Pooled advanced ADRs in the SFV and no SFV groups were 3.7 % and 2.5 %, respectively; RR (95 % CI) 1.45 (0.80,2.63), I2 = 0 %.

Right colon PDR with SFV vs no SFV

Four studies with 2893 patients were included in this analysis. Pooled PDRs in the SFV and no SFV groups were 33 % and 23 %, respectively; RR (95 % CI) 1.47 (1.30, 1.65), $I^2 = 0\%$ (▶ **Fig. 3**). Quality of evidence on GRADE framework was high (**Supplementary Table 2**).

Overall ADR with SFV vs no SFV

Four studies with 2403 patients were included in this analysis. Pooled ADRs in SFV and no SFV groups were 51.4 % and 46.7 %, respectively; RR (95 % CI) 1.10 (1.02, 1.19), I2 = 0 % (▶ **Fig. 4**). Quality of evidence on GRADE framework was high (**Supplementary Table 2**).

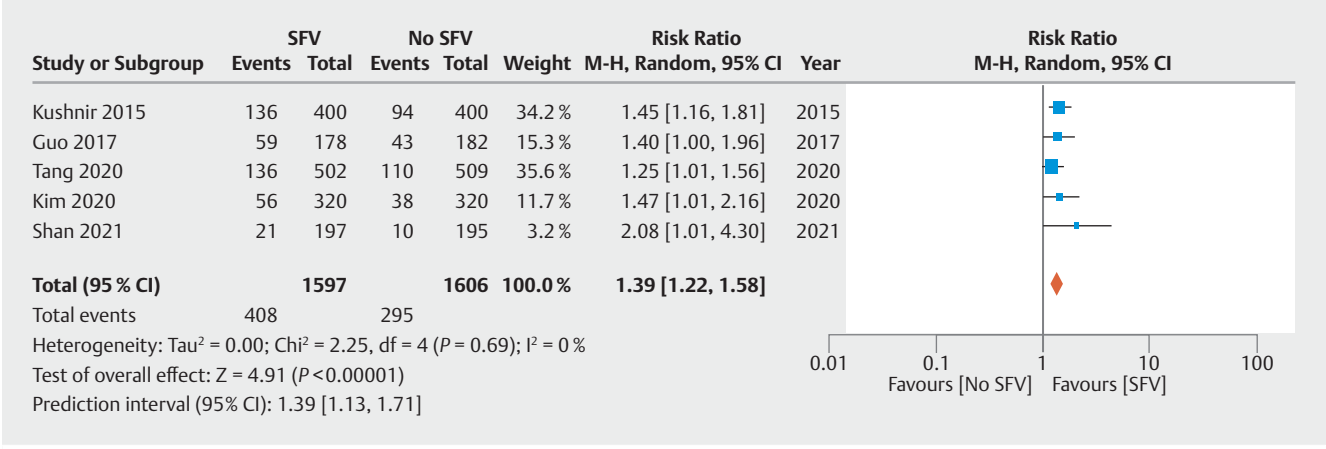
Withdrawal times

We found no significant difference in either right colon withdrawal time (SMD (95 % CI) 1.54 (-0.20, 3.28), $I^2 = 99\%$) (▶ **Fig. 5a**) or total withdrawal time (SMD (95 % CI) 0.37 (–0.39, 1.13), $I^2 = 98\%$) (▶ **Fig. 5b**) between SFV and no SFV. We also found no significant difference between time spent with SFV or RF in the right colon; SMD (95 % CI) 0.12 (-0.28, 0.52), $I^2 = 93\%$. Quality of evidence on GRADE framework was low (**Supplementary Table 2**).

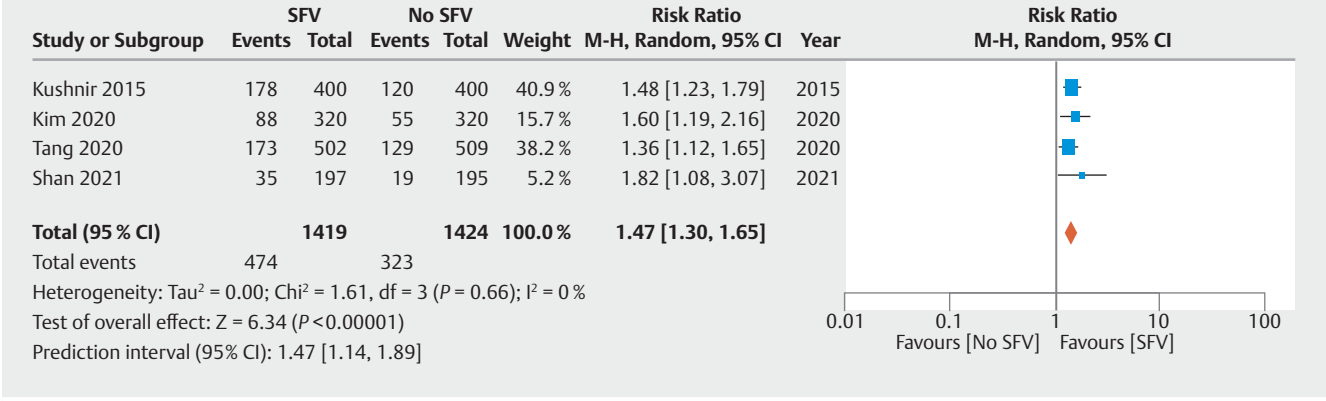
▶ **Table 1** Characteristics of included studies.

Study, year	No. patients	Comparison groups	Number (%) of males	Mean BMI	Mean age	Definition of right colon or proximal colon	Inclusion criteria	Exclusion criteria
Shan et al, 2021	392	SFV vs no SFV	213 (54%)	SFV: 23.2 ± 3.5 No SFV: 22.9 ± 3.1	SFV: 47.7 ± 12.6 No SFV: 46.1 ± 13.2	Cecum to hepatic flexure	Outpatients, 18 to 75 years old undergoing colonoscopy for screening or surveillance.	History of colon resection, IBD or polyposis syndromes, or poor bowel preparation (BBPS score < 2 in any segment of the colon). Unable to provide informed consent, did not successfully undergo cecal intubation, or were receiving active antithrombotic therapy preventing polypectomy.
Tang et al, 2020	1011	SFV vs no SFV	546 (54%)	SFV: 23.93.6 No SFV: 24 ± 3.8	SFV: 59.9 ± 8.4 No SFV: 59.8 ± 8.5	Cecum to hepatic flexure	Asymptomatic patients, 50 to 75 years of age undergoing colonoscopy for CRC screening or polyp surveillance.	Unable to provide informed consent, contraindications for endoscopy due to comorbidities, history of polyposis syndrome, IBD, prior colonic resection, irreversible coagulopathy and thrombocytopenia, incomplete colonoscopy due to failed cecal intubation, or a BBPS score of 0 in either right colon, transverse colon, or left colon preventing completion of procedure and adequate mucosal examination.
Kim et al, 2020	640	SFV vs no SFV	417 (65%)	SFV: 23.9 ± 3.1 No SFV: 24.5 ± 3.3	SFV: 53.5 ± 9.2 No SFV: 53.7 ± 8.6	Cecum to hepatic flexure	Asymptomatic subjects aged 40 to 70 years who underwent a screening colonoscopy.	Patients who refused to participate, patients with CRC, IBD, colonic polyposis, hereditary colon cancer, prior colonic resection of any part of the colon, or inability to give informed consent.
Nunez Rodriguez et al, 2020	648	SFV vs RF	360 (56%)	SFV: 27 ± 4.67 RF: 27.32 ± 4.63	SFV: 60.64 ± 5.76 RF: 59.74 ± 5.61	Cecum to hepatic flexure	Asymptomatic patients aged 50 to 69 years with a positive FIT (> 20 lg/g) referred by the CRC screening program who signed informed consent.	Patients who rejected giving informed consent, incomplete colonoscopy, inadequate preparation (right side colon BBPS < 2) or pathological findings: colorectal malignant neoplasm, diverticulitis, IBD or colonic stenosis.
Guo et al, 2017	360	SFV vs no SFV	197 (55%)	NA	SFV: 55.0 ± 11.0 No SFV: 54.9 ± 10.3	Cecum to the splenic flexure.	Patients aged ≥ 18 and ≤ 80 undergoing colonoscopy Patients with an intermediate or high risk of colorectal advanced neoplasia were enrolled according to Asia-Pacific CRC screening score (≥ 2).	Patients with advanced colonic cancer, prior resection of the proximal colon, IBD, polyposis syndrome, unable to provide informed consent. quality of bowel preparation was unsatisfactory (BBPS score < 2 in any segment of the colon) or if the cecum could not be intubated during the colonoscopy.
Kushnir et al, 2015	850	SFV vs RF	349 (41%)	SFV: 30.3 ± 7 RF: 29.3 ± 6.5	SFV: 59.0 ± 8.3 RF: 59.9 ± 8.3	Cecum to hepatic flexure	Patients undergoing colonoscopy for colorectal cancer screening or post-polypectomy surveillance.	Unable to provide informed consent, prior resection of the right colon, IBD, or the polyposis syndrome, if the cecum could not be intubated or if the quality of bowel preparation was inadequate (BBPS score < 2 in any segment of the colon).

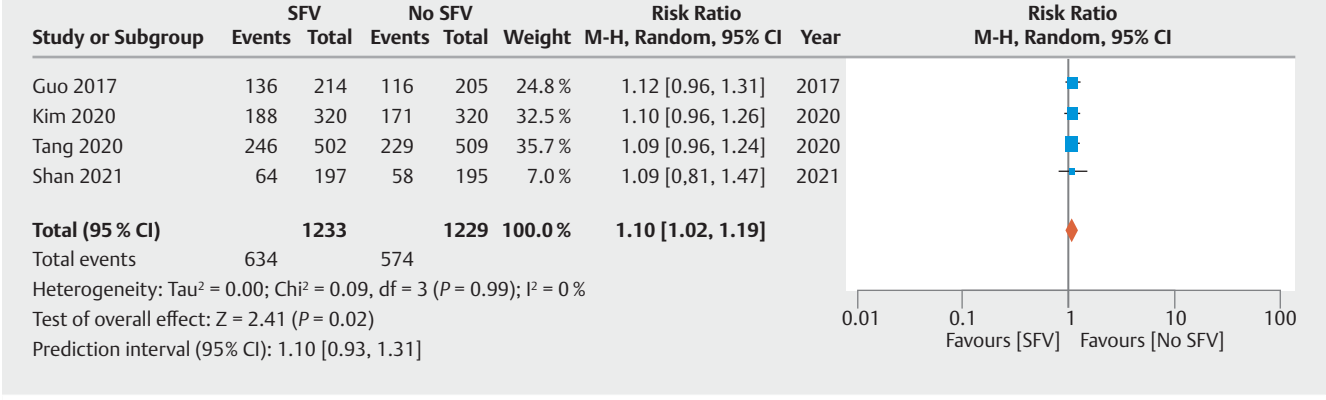
NA, not available; SFV, second forward view; RF, retroflexion; BBPS, Boston Bowel Preparation Scale; CRC, colorectal cancer; IBD, inflammatory bowel disease.



▶ **Fig. 2** Forest plot comparing right colon ADR between SFV and no SFV groups.



▶ **Fig. 3** Forest plot comparing right colon PDR between SFV and no SFV groups.



▶ **Fig. 4** Forest plot comparing overall ADR between SFV and no SFV groups.

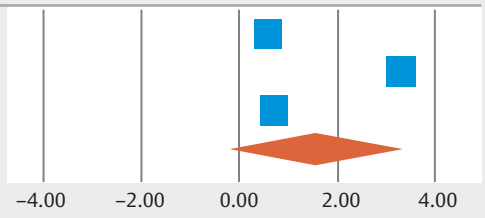
Additional ADR and PDR with RF vs SFV

Pooled additional ADRs with RF or SFV were 8 % and 11 %, respectively; RR (95 % CI) 0.74 (0.54, 1.01), I^2 = 0 % (**Supplementary Fig. 3**). Pooled additional PDRs with RF or SFV were 13 % and 18 %, respectively; RR (95 % CI) 0.76 (0.59, 0.97), I^2 = 0 % (**Supplementary Fig. 4**). Quality of evidence on GRADE framework was moderate to high (**Supplementary Table 2**).

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	*P*-Value
Kim 2020	0.600	0.081	0.007	0.442	0.759	7.428	0.000
Tang 2020	3.306	0.097	0.009	3.116	3.495	34.166	0.000
Guo 2017	0.714	0.109	0.012	0.501	0.927	1.738	0.082
	1.540	0.886	0.785	−0.196	3.276	1.738	0.082

Statistics for each study

Std diff in means and 95% CI



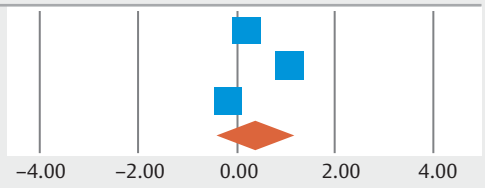
Prediction interval (95% CI): 1.54 [−20.90, 23.98]

a

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	*P*-Value
Kim 2020	0.199	0.079	0.006	0.043	0.354	2.506	0.012
Tang 2020	1.093	0.067	0.005	0.960	1.225	16.202	0.000
Guo 2017	−0.182	0.106	0.011	−0.389	0.025	−1.722	0.085
	0.373	0.387	0.150	−0.387	1.132	0.962	0.336

Statistics for each study

Std diff in means and 95% CI



Prediction interval (95% CI): 0.37 [−9.39, 10.13]

b

▶ **Fig. 5** Forest plot comparing withdrawal times between SFV and no SFV groups.

Discussion

SFV of the right colon during colonoscopy significantly increases the ADR in the right colon and overall. However, there was no significant difference in additional ADR between performing either SFV or RF in the right colon. The clinical relevance of these findings is that polyps in the right colon present a clinical challenge as they are often more difficult to detect during colonoscopy, which is less effective for the prevention of right-sided than left-sided cancer [6]. Therefore, a second inspection of the right colon with either SFV or RF affords an opportunity to increase ADR in the right colon and, by extension, to improve the ability to prevent right-sided colon cancer. Several modalities may also increase ADR such as cap-assisted colonoscopy [25], second-generation distal attachment cuff device [26], and third eye retroscopes [27]. However, these are inevitably associated with increased costs of the procedure. In contrast, SFV or RF in the right colon increase ADR at no additional cost.

We found that SFV of the right colon was associated with an 8% increase in right-sided ADR, which was statistically significant (pooled OR [95% CI] 0.67 [0.54,0.82]). Several studies have shown that RF in the right colon also increases ADR. One advantage of SFV over RF is that it can be performed safely in all patients and does not require additional skills. In contrast, RF requires additional skills and supervised training, and may not be achievable in all patients including those with tortuosity of the colon. One meta-analysis found that the rate of successful RF in the cecum was 92% [28]. Although RF in the proximal colon is generally considered safe, it may be associated with a slightly increased risk of perforation [28, 29]. Furthermore, we found no significant difference in additional ADR between SFV and RF. These findings support the use of SFV as the preferred modality of making a second examination of the right colon. It is also important to note that the increase in ADR with SFV exam of right colon is probably limited to small adenomas. We found no significant difference in advanced ADR between SFV and no SFV groups, RR (95% CI) 1.45 (0.80,2.63).

We found no significant differences in withdrawal times for the right colon or the entire colon when comparing SFV with no SFV. Second examination of the right colon could potentially increase procedure time and, in this regard, our results were unexpected. Although the absolute withdrawal times were slightly higher in the SFV group than the no SFV group, this difference did not reach statistical significance. However, lack of statistical significance is not an indication of equivalence. Also, the analyses of withdrawal times were limited by considerable heterogeneity, and the quality of evidence was low. Because of these limitations, firm conclusions cannot be made about withdrawal times.

One previous meta-analysis [30] that included both observational studies and RCTs found that SFV was associated with a higher additional right-sided ADR compared to RF, which is in contrast with our findings. However, those authors included the study by Rath et al [31] in which RF was performed in all parts of the colon rather than just the proximal colon. As previously noted, we excluded that study from our analysis for the reason stated. We did not perform an analysis of AMR as it was performed in a previous meta-analysis [30]; consequently, we excluded the RCT by Harrison et al [23] because it reported AMR rather than ADR. Lv et al [30] found no significant difference in AMR between RF and SFV.

The major strength of our meta-analysis is that it was restricted to RCTs only. RCTs represent the highest level of evidence. There was low heterogeneity in most of our analyses, except for those of withdrawal times. Our findings remained robust in a pre-determined sensitivity analysis. Our meta-analysis also has several limitations. In all studies except one [20], the SFV examination was performed from the hepatic flexure to the cecum. The exception was the study by Guo et al [20], in which the SFV examination was performed from the splenic flexure to the cecum. To address this, we performed a sensitivity analysis that excluded that study, and found consistent results. The analysis of additional ADR when comparing right colon SFV with RF was necessarily limited as there were only two studies. There was some clinical heterogeneity among studies. Nunez Rodriguez et al [19] only included patients with a positive fecal immunochemical test. In the study by Shan et al [18], all patients underwent colonoscopy without sedation. Most studies included patients who underwent either screening or surveillance colonoscopy. However, Kim et al [16] only included patients having screening colonoscopy. Serrated PDR is also a predictor of post-colonoscopy colorectal cancer [32]. Only one of the included studies in our meta-analysis reported data on the detection rate of serrated lesions. Therefore, we could not perform an analysis of this potential outcome.

Conclusions

In conclusion, SFV of the right colon increases right-sided and overall ADR. RF in the right colon does not offer additional benefit in increasing ADR than SFV. Although a second exam of the right colon may increase procedure time, its benefits in improving ADR should still outweigh this. Because SFV of the right colon requires no additional skills and is easier to perform than RF, it can be considered in clinical practice.

Competing interests

The authors declare that they have no conflict of interest.

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