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META-ANALYSIS

Diagnostic yield of third eye retroscope on adenoma detection during colonoscopy: A systematic review and meta-analysis

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Abstract

AIM: To determine the diagnostic yield of the "third eye retroscope", on adenoma detection rate during screening colonoscopy.

METHODS: The "third eye retroscope" when used with standard colonoscopy provides an additional retrograde view to visualize lesions on the proximal aspects of folds and flexures. We searched MEDLINE (PubMed and Ovid), SCOPUS (including MEDLINE and EMBASE databases), Cochrane Database of Systemic Reviews, Google Scholar, and CINAHL Plus databases to identify studies that evaluated diagnostic yield of "third eye retroscope" during screening colonoscopy. DerSimonian Laird random effects model was used to generate the overall effect for each outcome. We evaluated statistical heterogeneity among the studies by using the Cochran Q statistic and quantified by I^2 statistics.

RESULTS: Four distinct studies with a total of 920 patients, mean age 59.83 (95%CI: 56.77-62.83) years, were included in the review. The additional adenoma detection rate (AADR) defined as the number of additional adenomas identified due to "third eye retroscope" device in comparison to standard colonoscopy alone was 19.9% (95%CI: 7.3-43.9). AADR for right and left colon were 13.9% (95%CI: 9.4-20) and 10.7 (95%CI: 1.9-42), respectively. AADR for polyps $\geqslant$ 6 mm and $\geqslant$ 10 mm were 24.6% (95%CI: 16.6-34.9) and 24.2% (95%CI: 12.9-40.8), respectively. The additional polyp detection rate defined as the number of additional polyps identified due to "third eye retroscope" device in comparison to standard colonoscopy alone was 19.8% (95%CI: 7.9-41.8). There were no complications reported with use of "third eye retroscope" device.

CONCLUSION: The "third eye retroscope" device when used with standard colonoscopy is safe and detects 19.9% additional adenomas, compared to standard colonoscopy alone.

Key words: Third Eye Retroscope; Screening colonoscopy; Adenoma detection rate; Polyp detection rate; Additional adenoma detection rate; Additional polyp detection rate

Core tip: Missed lesions remain one of the main causes for development of interval colorectal cancer after screening colonoscopy. The third eye retroscope (TER) provides an additional retrograde view to visualize lesions on the proximal aspects of folds. In this meta-analysis of four studies including 920 patients undergoing screening colonoscopy, we observed that the additional adenoma detection rate, defined as the number of additional adenomas identified due to TER device in comparison to standard colonoscopy alone, was 19.9% (95%CI: 7.3-43.9). We found that TER device was safe and identified significant more numbers of adenoma which would have been missed by standard colonoscopy alone.

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INTRODUCTION

Colorectal cancer is the third most frequent cancer diagnosis and the second leading cause of cancer death in the United States[1]. As the disease exhibits a characteristic sequence of progression from precancerous adenomas to carcinoma stage[2], colonoscopy has been recommended by the United States Preventive Services Task Force as one of the criterion standard for the detection as well as the removal of adenomas to halt the progression to malignancy[1,3,4]. However, despite meticulous techniques, adenoma miss rates as high as 5% to 24% have been reported[5-7], thus leading to the development of colorectal cancer within short intervals of completion of complete colonoscopy[8-11]. These lesions maybe missed due to suboptimal withdrawal technique, inadequate bowel cleansing or in some cases, impaired visualization due to flattened and depressed contour of the lesions. Another technical factor identified is the likelihood of missing lesions located on "blind spots" such as the proximal aspect of flexures or haustral folds, rectal and ileocecal valves and behind semilunar folds.

To circumvent this, Triadafilopoulos *et al*[12] evaluated an ancillary imaging device called the third eye retroscope (TER) (Avantis Medical Systems, Inc, Sunnyvale, CA) in anatomic models of colon with simulated polyps in 2007. This device provides a continuous backward or retrograde view that complements the forward view of the standard colonoscope as they are withdrawn together through the colon and thus enhances the visualization of hidden areas, which was supported by the increased adenoma detection rates with its use[13]. Subsequent trials have undertaken the use of TER in humans and have unanimously reported higher adenoma detection rates, especially for smaller sized lesions with moderate increase in procedure times and no predilection for occurrence of complications[14-16]. This finding is clinically significant as adenoma detection rate has been proven as an independent predictor for development of interval colorectal cancer after screening colonoscopy[17]. The aim of the study was to systematically review and perform a meta-analysis regarding the clinical impact of TER on adenoma detection.

MATERIALS AND METHODS

Search strategy

The systemic review was performed according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[18]. We queried MEDLINE (PubMed and Ovid from 1990 to April 2014), SCOPUS, Cochrane Database of Systemic Reviews, Google scholar, and CINAHL Plus databases for eligible studies using the search term "Third Eye Retroscope" or "Retroscope" or "Retrograde colonoscopy" or "Retrograde viewing device". In addition, references of eligible articles retrieved by online search were reviewed for the eligible studies by the investigators. Only articles describing findings on human subjects were included. The screening and data abstraction were performed by two independent investigators (N.T. and B.R.) according to inclusion and exclusion criteria, which were pre-defined in this study. We resolved differences by discussion with third investigator (S.G.).

Study characteristics

Inclusion criteria: The study population consisted of patients undergoing colonoscopy for screening or surveillance after previous polypectomy.

Intervention: The intervention was standard colonoscopy or standard colonoscopy with the use of TER.

Study design: Studies where the findings of standard colonoscopy were compared against the results of standard colonoscopy with TER, performed in the same patient, were included in the analysis.

Outcome: The main outcome of the study was to evaluate TER on the following parameters: Additional polyp detection rate (APDR) and Additional adenoma detection rate (AADR). The additional adenoma/polyps were defined as lesions which can be detected only by the TER. Any lesion which was visible on both TER and colonoscope was attributed to standard colonoscope and was not counted among the TER associated additional lesions.

Exclusion criteria: We excluded case reports, case series and review articles.

Table 1 Characteristics of included studies

Ref.	Location	Study design	Mean patient age (yr)	Sample size	Intervention	Quality score	ΔTER/SC		ΔTER / SC mean size (range) mm		Mean time (min)	
							Polyps	Adenoma	Polyps	Adenoma	Withdrawal	Total
Triadafilopoulos *et al*[16] 2008	United States	Prospective, Single center study	64 ± 9.6	(T): 24 (M): 16 (F): 8	SC + TER	23	4/34	1/8	7.5 (2-7)/ 4 (1-15)	7/8 (4-15)	NA	NA
Waye *et al*[14] 2010	United States	Prospective, Multicenter study	63.1 ± 6.5	(T): 249 (M): 132 (F): 117	SC + TER	22	34/257	15/136	5.2 (2-12)/ 4.4 (1-15)	NA	10.9	26
DeMarco *et al*[15] 2010	United States	Prospective, Multicenter study	56.8 ± 11.3	(T): 298 (M): 144 (F): 154	SC + TER	22	27/182	16/100	6.5 (2-13)/ 5.5 (1-40)	6.8 (2-13)/ 6.5 (1-40)	9.9 ± 4.1	24.7 ± 9.7
Leufkens *et al*[13] 2011[1]	Europe and United States	Randomized controlled trial, Multicenter study	Group A: 57.9 ± 9.7	(T): 173 (M): NA (F): NA	SC → SC + TER	23	78/160	49/107	NA	NA	9.52/7.58	20.87/16.97
			Group B: 58.2 ± 9.7	(T): 176 (M): NA (F): NA	SC + TER → SC		31/163	52/121	NA	NA		

[1]Time TER/SC. SC: Standard colonoscopy; TER: Third eye retroscope; T: Total; F: Female; M: Male; NA: Not available.

Data abstraction

Data abstraction was performed by two independent investigators (N.T. and B.R.) using MS-EXCEL based standardized data forms (Microsoft Excel, Microsoft Corporation, Redmond, Wash). The following information was recorded from individual studies: (1) study characteristics: country, publication year, study methodology including design, sample size, standardization of measurement and the clinical context; (2) summary measures of Demographic features such as age, race and gender distribution of the study population; and (3) interventions: manufacture and type of the TER used in each study.

Assessment of risk of bias (Quality criteria)

Study eligibility and quality assessment were critically performed by three independent investigators (N.T., B.R., and S.B.). Any disagreements were adjudicated by a third investigator (S.G.) through discussion. We evaluated each study based on the inclusion and exclusion criteria as previously delineated. We used the Standards for the Reporting of Diagnostic Studies checklist to accurately report quality of our included studies[19].

Data synthesis and statistical analysis

For the purpose of this meta-analysis, APDR was defined as the number of additional polyps identified due to TER device in comparison with standard colonoscopy. The additional AADR was defined as the number of additional adenomas identified due to TER device in comparison with standard colonoscopy. Technical error was defined as percentage of the patients in which TER failed to provide sufficient quality retrograde images either related issues with the cap size, failure to retroflex after coming out of the biopsy channel or due to malfunction of the image processor. DerSimonian Laird random effects model was used to generate the overall effect for each outcome. The random-effects model is more infallible than the fixed effect model as it incorporates into the weighing scheme both intra-study and inter-study variations[20].

Inter-Study heterogeneity was assessed based on Cochran Q statistic and I^2 statistics[21], with I^2 values of 25%, 50% and 75%, being classified as low, moderate and high heterogeneity, respectively[22]. We assessed the impact of removing one study at a time and determined the change in magnitude, direction, and the standard error of the pooled effect size. Meta-regression was applied to further explore heterogeneity in the pooled studies. In addition, we assessed the robustness of our meta-analysis with regards to the publication bias by using several tests including Egger regression asymmetry test[23], and Fail-safe N tests[24]. Further, Funnel plot was constructed to evaluate the publication bias using standard error and event rate[25,26]. Finally, Trim and Fill method was used to test and adjust for any significant publication bias in our meta-analysis. All statistical tests were performed with the Comprehensive Meta-analysis version 2.0 (Biostat, Englewood, NJ). We considered $P < 0.05$ as statistically significant for this meta-analysis.

RESULTS

Literature search

A total of 12 articles were identified and reviewed in detail by using the search terms of "Third Eye Retroscope". Of these 12 articles; 1 study was on animal model, and 6 were either review articles or letters to the editor, and were excluded from the analysis. In total, 4 studies, 1 randomized controlled trial and 3 prospective studies were selected for this meta-analysis[13-16]. One additional study was a post hoc analysis of the included randomized trial and these study was also excluded from the analysis[27]. The PRISMA checklist for systematic review was reported on Supplementary Table 1. The characteristics along with the quality of the included studies are shown in Table 1.

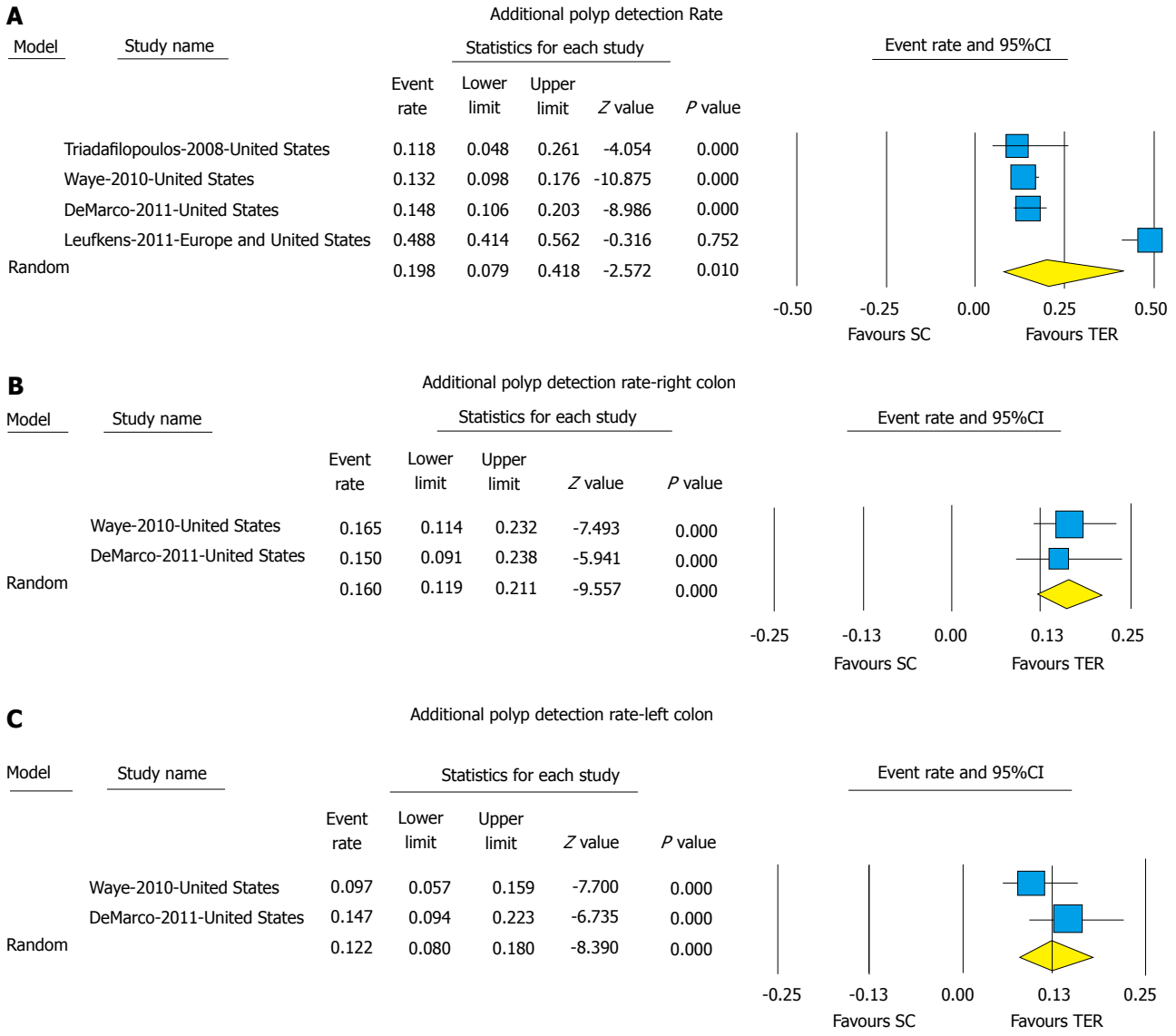

Figure 1 (A) Pooled additional polyp detection rate, (B) additional polyp detection rate-right colon, and (C) additional polyp detection rate-left colon with use of third eye retroscope compared to standard colonoscopy alone. The size of the each square is proportional to the sample size for each study, and the horizontal lines through the square indicate the 95%CI for that study. For the pooled analysis, the diamond indicated the pooled value and the right and left ends of the diamond indicate the 95%CI for the analysis. TER: Third eye retroscope; SC: Standard colonoscope.

Of the four studies included in the meta-analysis, Triadafilopoulos *et al*[12] found a total of 38 polyps with mean size of 4 ± 3 mm. Resected polyps consisted of 9 adenomatous polyps and 29 hyperplastic polyps. Of the 38 polyps, 30 polyps were detected in antegrade view, 4 in both antegrade-retrograde views, and TER helped in detection of 4 polyps that were located in the proximal aspect of the haustrae and visible only in retrograde view. Thus use of TER led to incremental yield of standard colonoscope (SC) by 11.8% through detection of additional polyps: 3 hyperplastic polyps (sizes: 2 mm, 3 mm, and 3 mm) and one tubullovillous adenoma (size: 7 mm). DeMarco *et al*[15] in demonstrated that TER detected 27 (14.8%) polyps in addition to 182 polyps detected with SC. While, 100 adenomas were detected on SC, TER facilitated detection of 16 (16%) more adenomas ($P < 0.001$). In addition, the mean sizes of the polyps or adenomas detected with SC and TER were similar ($P = 0.37$ and $P = 0.87$, respectively) and subgroup analyses revealed 23% increment in detection of polyps 6 mm or larger. Similar to above findings, Waye *et al*[14] also found that polyps and adenomas detected by the TER were comparable in terms of size to those detected by SC. However, in a two arm comparison of SC with TER, Leufkens *et al*[13] demonstrated TER detecting higher number of advanced polyps and adenoacarcinomas.

Meta-analysis

The four studies recruited a total of 920 patients with a mean age of 59.83 (95%CI: 56.77-62.83) years. A total of 46 patients were excluded from the studies due to technical error/device malfunction, with overall technical error rate of 4.6% (95%CI: 2.2-9.3) in intention to treat analysis.

The results of the meta-analysis are shown in detail in Table 2. The pooled APDR due to TER device in comparison to standard colonoscopy was 19.8 % (95%CI:

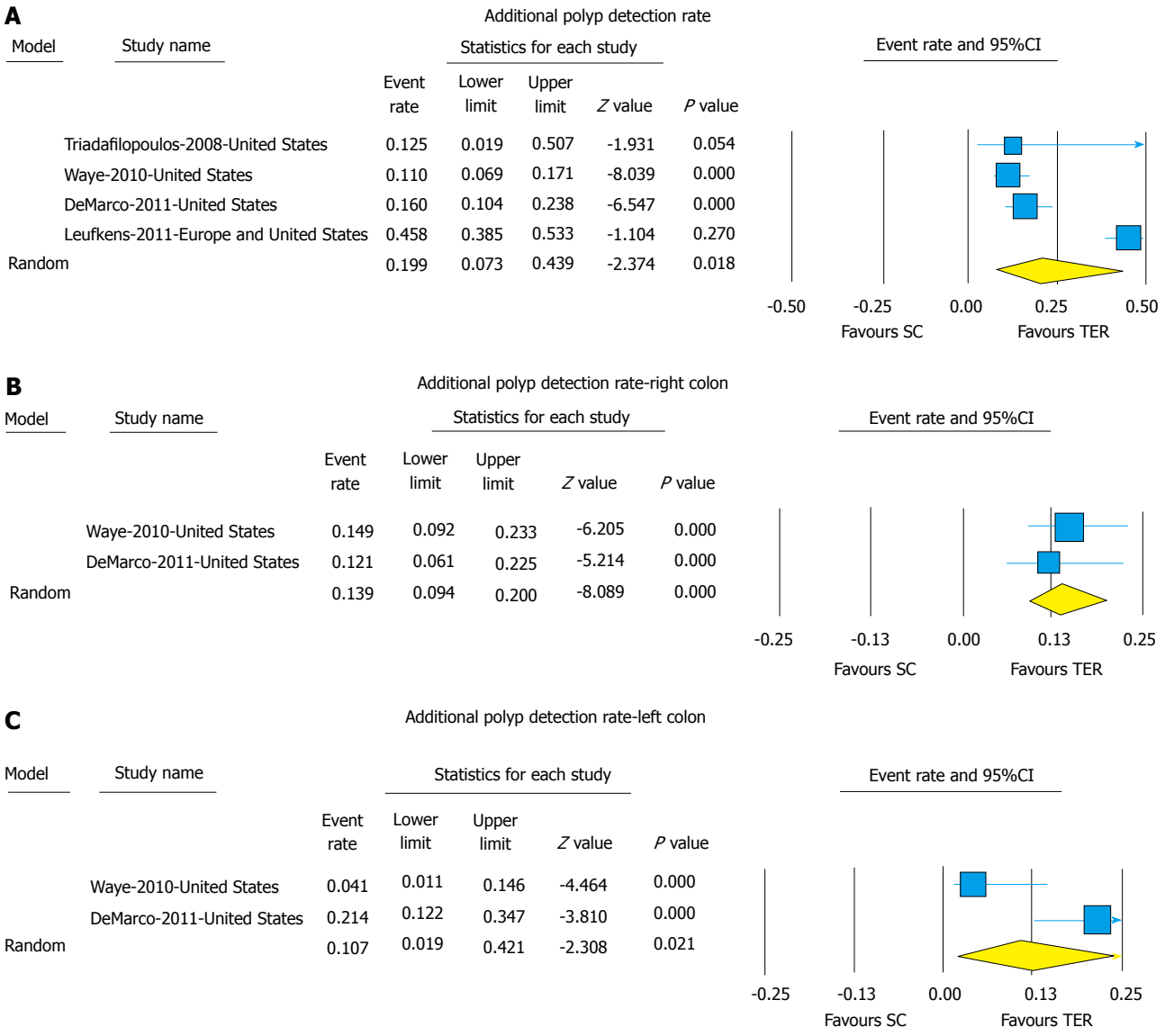

Figure 2 (A) Pooled additional adenoma detection rate, (B) additional adenoma detection rate-right colon, and (C) additional adenoma detection rate-left colon with use of third eye retroscope compared to standard colonoscopy alone. The size of the each square is proportional to the sample size for each study, and the horizontal lines through the square indicate the 95%CI for that study. For the pooled analysis, the diamond indicated the pooled value and the right and left ends of the diamond indicate the 95%CI for the analysis. TER: Third eye retroscope; SC: Standard colonoscope.

7.9-41.8) (Figure 1A). APDR for right colon and left colon was 16% (95%CI: 11.9-21.2) and 12.2% (95%CI: 8-18), respectively (Figures 1B and C). APDR for polyp ⩾ 6 mm in size was 20.9% (95%CI: 14.8-28.6) and for polyp ⩾ 10 mm in size was 25.3% (95%CI: 15.5-38.4).

The pooled AADR due to TER device in comparison to standard colonoscopy was 19.9% (95%CI: 7.3-43.9) (Figure 2A). AADR for right colon and left colon was 13.9% (95%CI: 9.4-20) and 10.7% (95%CI: 1.9-42), respectively (Figures 2B and C). AADR for polyp ⩾ 6 mm in size was 24.6% (95%CI: 16.6-34.9) and for polyp ⩾ 10 mm in size was 24.2% (95%CI: 12.9-40.8). There were no complications related to TER during the procedure.

The Funnel plots evaluating publication bias for both APDR and AADR are shown in Figure 3A and B. The Fail-safe N test showed that for the combined 2-tailed *P* value to be no longer significant ($P > 0.05$), it would need an additional 149 studies with "null" results. By using the random-effect model, the APDR and AADR were noted as 19.8% (95%CI: 7.9-41.8) and 19.9% (95%CI: 7.3-43.9), respectively and these values did not change using the Trim and Fill method.

DISCUSSION

Colonoscopy has so far been considered the best available method for colorectal cancer screening as it is sensitive and specific for detection of precancerous lesions. Yet, when the performance of colonoscopy have been evaluated with back to back colonoscopic examinations[5-7,28] or when compared with the results of CT colonography[29,30], colonoscopy has often been found to have missed a significant number of lesions. Two tandem colonoscopy studies reported adenoma miss rates of

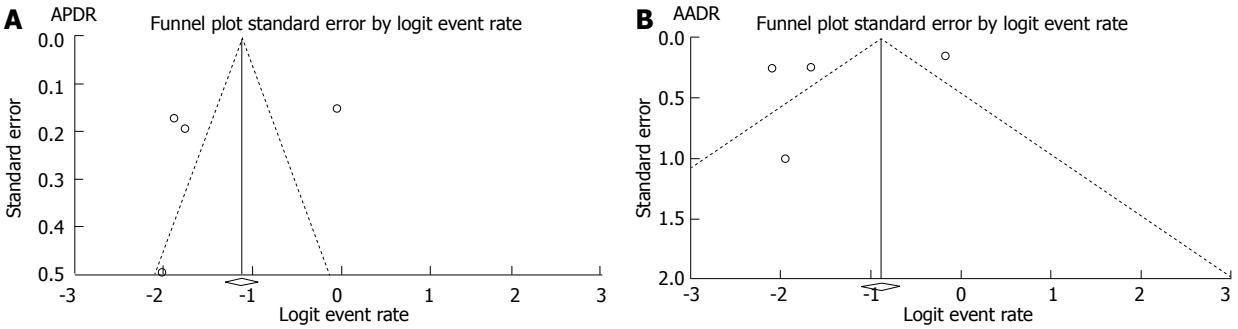

Figure 3 Funnel Plot for publication bias for (A) additional polyp detection rate and (B) additional adenoma detection rate.

Table 2 Results of meta-analysis: Additional polyp detection rate and additional adenoma detection rate

Category	No. of studies	Event rate (%)	95%CI	Heterogeneity	
				P	I^2 (%)
APDR	4	19.8	7.9-41.8	0	96.38
APDR right colon	2	16	11.9-21.2	0.76	0
APDR left colon	2	12.2	8-18	0.22	31.9
APDR 6 mm or more	2	20.9	14.8-28.6	0.47	0
PDR 10 mm or more	2	25.3	15.5-38.4	0.51	0
AADR	4	19.9	7.3-43.9	0	94.44
AADR right colon	2	13.9	9.4-20	0.61	0
AADR left colon	2	10.7	1.9-42	0.02	82
AADR 6 mm or more	2	24.6	16.6-34.9	0.94	0
AADR 10 mm or more	2	24.2	12.9-40.8	0.34	0

APDR: Additional polyp detection rate; AADR: Additional adenoma detection rate.

20%-24%[6,28]. A study comparing colonoscopy with CT colonography reported a colonoscopy miss rate of 12% for polyps 1 cm or larger[29]. In addition, colon cancer had been diagnosed within a short interval after a meticulous colonoscopy[31,32]. These studies shed light on missed lesions after standard colonoscopy and raise the issue that colonoscopy is a less sensitive screening tool than previously perceived, with profound clinical and medico-legal implications[33-35].

Factors contributing to the colonoscopy miss rates include operator related variables such as lower level of expertise, sub optimal withdrawal technique[36], decreased observation time during extubation[36-40] and other technical factors such as poor bowel preparation[36,41-43] and inadequate visualization of all areas[29,36]. Pickhardt *et al*[29] identified that 67% of the adenomas that were missed by colonoscopy but had been picked up by CT colonography were located on the proximal aspect of folds, which account for 7.8% of colon surface area[44]. Another study concurred that lesions located on the proximal aspect of colonic mucosal or haustral folds, behind the rectal valves, beneath the ileocecal valve, or on the inner curve of flexures are difficult to detect with a forward-viewing colonoscope, even with various manipulations[45]. To enhance exposure of mucosa in these "hidden areas", TER has been evaluated with promising results[10-14].

The TER system consists of 3 parts: the retroscope, a cap with a polarizing filter, and a dedicated video-image processor. After the standard colonoscope is advanced into the cecum, the retroscope is inserted through the "working channel" of the colonoscope until it extends beyond its other end. Since the distal tip of the TER naturally assumes a bent "J" shape after emerging from channel, it provides 180-degree retrograde illumination and visualization of the colon when the standard colonoscope is withdrawn. In comparison to TER, standard colonoscope only provides 140-degree field of view during examination. During its initial evaluation in an anatomic model with simulated polyps, the use of TER contributed to greater visualization of simulated polyps placed on obscure locations including behind the folds when compared to the standard colonoscope alone (81% *vs* 12%, $P = 0.00001$)[12]. Also TER improved visualization of colonic mucosal surface area from 87% to 99% when used in conjunction with a standard colonoscope, thus facilitating enhanced detection of lesions[46].

This enhanced detection is gauged by two parameters - APDR and AADR. Our analysis has showed APDR of 19.8 % (95%CI: 7.9-41.8) and AADR of 19.9% (95%CI: 7.3-43.9) with the use of TER device in comparison to standard colonoscopy alone. These additional polyps were detected in both right and left colon (16% *vs* 12.2%) and a similar observation was also made for adenoma detection in both right and left colon (13.9% *vs* 10.7%). This diagnostic benefit provided by the TER is of clinical importance, since standard colonoscopy has been reported to be less protective for right sided colorectal cancer[8,47]. With the use of TER, the APDR and AADR for polyps greater than $\geqslant$ 10 mm in size was 25.3% and 24.2 % respectively. These lesions have been shown to have a greater likelihood for malignant transformation[48,49] and hence their detection and removal would enhance the efficacy of screening colonoscopy.

Some technical difficulties with the use of the device have been noted including the inability to advance the catheter through the "working channel", inadequate clasping onto the cap and kinking of the retroscope. These device related reasons led to the exclusion of 20 patients in the 4 studies. However no procedural complications or device related safety issues were reported, although the use of TER was avoided in patients with potential risk factors including ulcerative colitis or Crohn's disease, familial adenomatous polyposis, and severe di-

verticulosis[14,15].

Some of the disadvantages of using a TER include the inferior image quality[50], the impaired ability to aspirate luminal contents[50] and the increase in the withdrawal and procedure time, which may be attributed to the time required for removal and reintroduction of the auxiliary device when a polyp is encountered[51] and partly due to the increased number of polypectomies[13]. However with increasing endoscopist's experience with the device, significant decreases in withdrawal times and total procedure times have been noted[15]. Although the polarizing filter minimizes the blinding of the retroscope's image by the colonoscope's light, residual glare has been reported as a minor distraction[12]. In order to diminish this effect, a short period of adjustment is necessary to adapt to the side-by-side viewing of images with distinctive directional orientations[50].

In the TER system, the cap and catheter are single use only and a large initial investment is necessary for acquiring the video processor. The post hoc analysis performed on the TERRACE trial showed that the AADR with TER for screening colonoscopy was only 4.4%, whereas for surveillance and diagnostic colonoscopy it was 35.7% and 55.4% respectively[27]. When this modest improvement in the diagnostic yield of screening colonoscopy is weighed against the cost of performing the procedure, the benefit of using the TER in routine clinical practice is brought to question. Results of this meta-analysis will help future cost-effectiveness analysis to determine routine use of TER.

In summary, the results from this systematic review suggest that the TER is a safe and promising tool for enhancing the efficacy of the standard colonoscope for detection of colonic polyps and adenomas. This device allows retrograde views of the proximal parts of colonic mucosal or haustral folds, back of the flexures and thereby increased diagnostic yield of identifying adenomatous polyps by almost 20%.

COMMENTS

Background

Colorectal cancer is the third most frequently diagnosed cancer and the second leading cause of cancer death in the United States. Colonoscopy facilitates early detection of adenomatous polyps in colon and therefore has been recommended by the United States Preventive Services Task Force as a screening tool for prevention of colorectal cancer. However, despite several improvements in the colonoscope design and operator performance, up-to one fourth of adenomas are missed and could lead to increase in the risk of colorectal cancer. These lesions maybe missed due to various reasons including being located on 'blind spots' such as the proximal aspect of flexures or haustral folds, rectal and ileocecal valves and behind semilunar folds. Third eye retroscope (TER) is an attachment to standard colonoscope which allows endoscopist to inspect regions of the colon not visible to standard colonoscope. The published evidence for the benefit of this device has been equivocal and limited mostly to small studies. The current study undertakes a systematic review of the existing evidence regarding the benefit of using TER attachment with standard colonoscopy and performs a meta-analysis of adenoma and polyp miss-rate to summarize the results.

Research frontiers

The meta-analysis evaluates the hypothesis that third eye retroscope reduces the polyp and adenoma miss-rate when used in conjunction with the standard colonoscope. In addition, the study determines the safety of the device.

Innovations and breakthroughs

The key findings of the study indicate that use of third eye retroscope attachment significantly improves the adenoma detection and reduces the risk of colorectal cancer over the standard colonoscope. The results show that this device when used with standard colonoscopy is safe and detects 19.9% additional adenomas, compared to standard colonoscopy alone.

Applications

TER is a safe device and its use in addition to standard colonoscopy can make latter a more effective screening tool to prevent colorectal cancer.

Terminology

Third eye retroscope is a linear device that can be easily passed through the working channel of standard colonoscope. Since the distal tip of the TER naturally assumes a bent "J" shape it provides 180-degree retrograde illumination and visualization of the colon when the standard colonoscope is withdrawn. It has a video processor to capture images. Randomized clinical trial is a clinical trial which assigns treatments to patients randomly to compare effectiveness of two treatments. It is a gold standard of comparing treatments. Meta-analysis is a method of combining treatment effects from several studies in order to derive more conclusive and robust result on efficacy of treatments.

Peer review

This was a well-written article.

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