



## Review Article

# Impact of new techniques on adenoma detection rate based on meta-analysis data

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### ABSTRACT

The high incidence of colorectal cancer and the occurrence of interval cancers after screening colonoscopy support the need to develop methods to increase adenoma detection rate (ADR). This review focuses on the importance of ADR and the impact of new techniques on ADR based on meta-analysis data. The low-cost interventions (such as water-aided colonoscopy, second observation, and dynamic position change) were effective in increasing ADR. So were enhanced imaging techniques and add-on devices. Increase with higher cost interventions such as newer scopes is uncertain. Water exchange (WE) has the highest ADR compared with water immersion, air insufflation, and carbon dioxide insufflation. Second observation with forward or retroflexed views improved the right colon ADR. Add-on devices result in only modest improvement in ADR, of particular help in low performing endoscopists. The second-generation narrow-band imaging (NBI) provided a two-fold brighter image than the previous system. The improvement in ADR with NBI required the “best” quality bowel preparation. New endoscopic techniques incur various additional costs, nil for WE, small for tip attachments but large for the newer scopes. In conclusion, one or more of the above methods to improve ADR may be applicable in Taiwan. A comparison of these approaches to determine which is the most cost-effective is warranted.

**KEYWORDS:** Adenoma detection rate, Colonoscopy, Meta-analysis, Water exchange

## INTRODUCTION

Colorectal cancer is the second-most common cause of cancer-related deaths in the world. The natural history of colorectal cancer carcinogenesis through the adenoma-carcinoma sequence permits screening program to detect and remove pre-cancerous lesions. Colorectal cancer screening using fecal occult blood tests reduces the relative risk (RR) of mortality by up to 16% [1]. Currently, screening strategies for colorectal cancer, including annual and biennial guaiac-based fecal occult blood tests, annual and biennial fecal immunochemical tests, colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, and computed tomographic colonography every 5 or 10 years were cost-effective compared with no screening [2].

Because the incidence of colorectal cancer in Taiwan is among the highest in the world [3], the government has initiated the Taiwanese Nationwide Colorectal Cancer Screening Programme since 2004. The program offers biennial fecal immunochemical testing to average-risk subjects 50–74 years old, followed by colonoscopy for those who test positive. The screening program is effective in reducing the mortality from colorectal cancer [4]. Interval cancers, defined as cancers

diagnosed within 3–5 years after colonoscopy, however, still occur after colonoscopy in Taiwan [5] as in Western countries [6]. The occurrence of interval cancers has been linked to a low adenoma detection rate (ADR), defined as the proportion of patients with at least one adenoma. Corley *et al.* reported that for each 1% increase in ADR, there was 3% decrease in the risk of interval cancers and 5% decrease in fatal interval cancers [6]. A variety of techniques have been proposed to increase ADR with varying results. The current review summarizes the results of meta-analyses to provide evidence-based guidance for colonoscopists who are interested in increasing their ADR.

## WHY WE NEED ENDOSCOPIC TECHNIQUES TO IMPROVE ADENOMA DETECTION RATE?

A recent report showed the adenomas, and advanced adenomas are missed more frequently than previously believed [7].

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In a meta-analysis including 43 publications with 15,000 tandem colonoscopies, Zhao *et al.* reported the miss rates of 26% for adenomas, 9% for advanced adenomas, and 27% for serrated polyps. Miss rates were high for proximal advanced adenomas (14%; 95% confidence interval [CI] 5%–26%), serrated polyps (27%; 95% CI 16%–40%), flat adenomas (34%; 95% CI 24%–45%), and in patients at high risk for colorectal cancer (33%; 95% CI 26%–41%) [7]. The missed adenomas probably contribute to the occurrence of interval cancers. In a systemic review included a total of 117,793 patients with 7281 interval cancers (6.2%), the ADR of the endoscopist performing the index examination was the most consistent factor associated with the development of interval cancers [8]. Therefore, how to achieve a higher ADR has become a main issue for colorectal cancer prevention.

On the other hand, the achievement of a high ADR indeed decreases the risk of interval cancer. In a prospective study involving 294 endoscopists within the National Colorectal Cancer Screening Programme in Poland, reaching or maintaining the highest quintile ADR category (i.e., an ADR >24.56%) decreased the adjusted hazard ratios for interval cancer to 0.27 (95% CI, 0.12–0.63;  $P = 0.003$ ), and 0.18 (95% CI, 0.06–0.56;  $P = 0.003$ ), respectively, compared with no increase in ADR [9].

### COMPARING THE EFFICACIES OF DIFFERENT ENDOSCOPIC TECHNIQUES IN ADENOMA DETECTION

Several studies tried to show a decrease in the adenoma miss rate by improving bowel preparation or applying new endoscopic techniques [10]. These endoscopic techniques included add-on devices (cap, Endocuff, and EndoRings), enhanced imaging techniques (chromoendoscopy, narrow-band imaging [NBI], flexible spectral imaging color enhancement, and blue laser imaging), new scopes (full-spectrum endoscopy, extra-wide-angle-view colonoscopy, dual focus, and G-EYE), and low-cost optimizing existing resources (water-aided colonoscopy, second observation, and dynamic position change).

Among these endoscopic techniques, low-cost interventions, add-on devices, and enhanced imaging techniques are associated with significant improvement in ADR over high-definition colonoscopy alone; newer scopes did not show clear benefit over high-definition colonoscopy. One systematic review and network meta-analysis with 74 two-arm trials and a total of 44,948 patients by Facciorusso *et al.* confirmed the superiority of the use of add-on devices (odds ratio [OR], 1.18; 95% CI, 1.07–1.29), enhanced imaging techniques (OR, 1.21; 95% CI, 1.09–1.35), and low-cost optimization of existing resources (OR, 1.29; 95% CI, 1.17–1.43) over high-definition colonoscopy alone for increasing ADR [11]. The use of newer scopes was not associated with significant increases in ADR compared with high-definition colonoscopy (OR, 0.98; 95% CI, 0.79–1.21). No specific group of technologies for increasing ADR was superior to the others. There are no differences between groups of technologies in the detection of advanced ADR, polyp detection rate, or mean number of adenomas per patient.

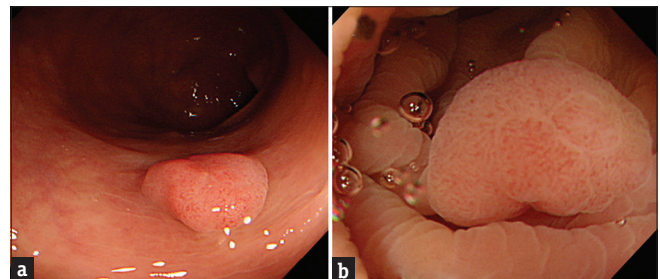
### LOW-COST INTERVENTIONS

Several low-cost interventions may increase the diagnostic yield of colonoscopy. New understanding of the mechanism of action of water exchange (WE) was elucidated recently [12]. Improved bowel preparation, the magnification effect of looking through water, and reduced withdrawal cleaning-related multitasking distractions were plausible mechanisms by which WE improved ADR [Figure 1] [12,13]. Repeated examinations of the right colon, either forward or retroflexed, may help to identify more adenomas [14–16]. Dynamic position changes during withdrawal were reported to provide adequate distention for observation at different colonic segments and could be an effective method to significantly increase ADR [17,18]. The meta-analyses demonstrating the benefits of WE colonoscopy and second observation are discussed below [6,18–22].

#### Water exchange colonoscopy

Water-aided colonoscopy is a low-cost technique by optimizing existing resources. Renewed interest has been demonstrated in the literature for water-aided colonoscopy techniques [13,23], which are distinguished by the timing of removal of infused water, predominantly during withdrawal (water immersion [WI]), or during insertion (WE) [13] [Figure 2]. Due to salvage cleansing effect by the water, WE could provide a higher quality of the bowel preparation as compared with air insufflation (AI) and WI, thereby improving the endoscopic views and the detection of adenomas [21]. During the insertion phase of WE, clean water is infused to guide scope advancement and removed almost simultaneously, allowing for less distractions caused by washing the mucosa and suctioning the dirty water during the withdrawal phase. A recent reviewer-blinded analysis of video recordings suggested that reduced cleaning-related multitasking distractions during withdrawal and not bowel preparation quality underpinned the association between increased ADR and WE [12].

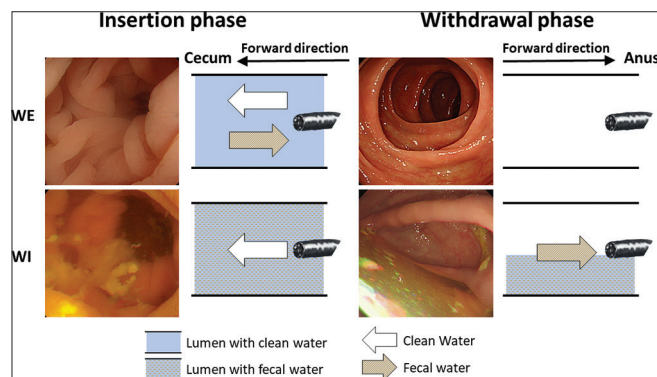
Four meta-analyses studies confirmed that WE yielded the highest ADR compared with WI, AI, and carbon dioxide insufflation [Table 1] [13,19–22]. Fuccio *et al.* conducted a network meta-analysis which included 17 trials with 41 study arms and 10,350 patients. The raw estimates of overall ADR were as follows: 41.7% (95% CI, 32.5%–51.5%) for WE, 34.4% (95% CI, 28.3%–40.9%) for WI, 30.2% (95% CI, 24.4%–36.8%) for AI, and 31.1% (95% CI, 19.0%–46.4%) for carbon dioxide



**Figure 1:** The impact of water exchange on the image of a polyp. (a) One flat polyp was noted in the standard colonoscopy. (b) During the water exchange colonoscopy, the magnification effect of water made the polyp more conspicuous

insufflation. WE had a significantly higher entire colon overall ADR when compared with WI, air, and carbon dioxide insufflation [Table 1]. ADR of the right side of the colon was 21.1% (95% CI, 16.4%–26.8%) for WE, 15.8% (95% CI, 12.5%–19.8%) for WI, and 14.2% (95% CI, 11.6%–17.3%) for AI. WE showed a significantly higher ADR in the right side of the colon than AI and WI [Table 1]. In subgroup analyses, WE achieved the highest ADR also in colorectal cancer screening cases (significant vs. AI and WI); in patients conducted with split-dose bowel preparation (significant vs. AI, WI and carbon dioxide insufflation). Similar beneficial effects were also demonstrated in the Bayesian meta-analysis by Zhang *et al.* [19], in which AI, carbon dioxide insufflation, and WI had a significantly lower ADR compared with WE.

Two meta-analyses assessed whether the ADR of WE was superior to that of WI [Table 1]. Both found WE had higher overall ADR and right colon ADR than WI [20,22]. Chen *et al.* reported WE showed a significantly higher ADR in the entire colon (RR = 1.18; CI = 1.05–1.32;  $P = 0.004$ ) and in the right colon (RR = 1.31; CI = 1.07–1.61;  $P = 0.01$ ) than WI [Table 1]. The Bayesian network meta-analysis by Shi *et al.* [20] showed that, compared with WI colonoscopy, WE colonoscopy significantly improved the ADR (RR: 1.2, 95% credible interval: 1.1–1.3). The different methods were ranked in order from the most to the least effective in adenoma detection as follows: WE, WI, AI, and carbon dioxide insufflation [20]. In propofol sedated patients, WE (38.9%) had significantly higher overall ADR than AI (26.7%) [24].



**Figure 2:** Water-aided colonoscopy. During the insertion phase of water exchange (top panels) and water immersion (bottom panels), clean water is infused to guide the advance of colonoscope. The infused water is removed almost simultaneously and completely during insertion with water exchange, while it is removed mainly during withdrawal with water immersion. Gas is insufflated to distend the lumen for inspection during withdrawal. The salvage cleaning effects of water exchange improve the bowel preparation and avoid multitasking distractions during withdrawal

Because WE required times for the removal of infused water, residual air, and feces, it does prolong the procedure time. The insertion time was reported by a network meta-analysis, which included 17 trials with 41 study arms and 10,350 patients [21]. The result showed that WE has the longest insertion time (3–5 additional minutes), but the withdrawal time was comparable with other methods [21]. Cecal intubation time was 13.4 min (95% CI, 9.1–17.7 min) for WE, 8.3 min (95% CI, 7.4–9.2 min) for WI, 10.2 min (95% CI, 6.6–13.8 min) for AI, and 8.5 min (95% CI, 6.8–10.2 min) for carbon dioxide insufflation. WE required significantly longer cecal intubation time, as compared with AI, carbon dioxide insufflation, and WI. WI did not differ from both AI and CO<sub>2</sub> insufflation. Withdrawal time was reported by 9 trials (22 study arms, 7007 patients) and was not significantly different among the 4 colonoscopy techniques. A recent meta-analysis showed that the increase of the procedure time was a few minutes (WE 26.0 ± 9.7 vs. AI 24.2 ± 9.6, with a mean difference of 1.8 ± 6.2 min) [25].

### Second observation with forward or retroflexed views

Two meta-analyses assessed the effect on ADR by a second examination of the right colon with forward-view or retroflexion immediately after the initial examination. Both tandem forward and retroflexed views improved the right colon ADR [15,16]. Ai *et al.* combined six cohorts of five studies with 4155 participants and found the right colon ADR was 28.8% with a second examination compared with 24.1% with a single examination ( $P < 0.001$ ), for a pooled OR of 1.34 (95% CI: 1.13–1.59) [16]. Desai combined five trials with 1882 patients who underwent either a second forward view or a retroflexed view of the right colon after the initial standard colonoscopy [15]. The second forward view of the right colon increased the right colon ADR by 10% (4 trials, 33.6% vs. 26.7%). Retroflexion increased the right colon ADR by 6% (3 trials, 28.4% vs. 22.7%). There was no statistically significant difference in adenoma miss rate between second examinations with forward view and with retroflexion. In short, a tandem examination, in either a forward or a retroflexed view, could lead to a modest improvement in the right colon ADR. However, the second examination means longer observation and procedure time. The gain in ADR would be at the cost of increased procedure time.

### ADD-ON DEVICES

Several add-on devices (such as cap, Endocuff, and EndoRing) [Figure 3] [26] have been developed to increase ADR. They could hold away and flatten the colonic folds during withdrawal, allowing for better visibility behind the

**Table 1: Summary of meta-analyses studies about the impact of the water exchange colonoscopy on adenoma detection rate**

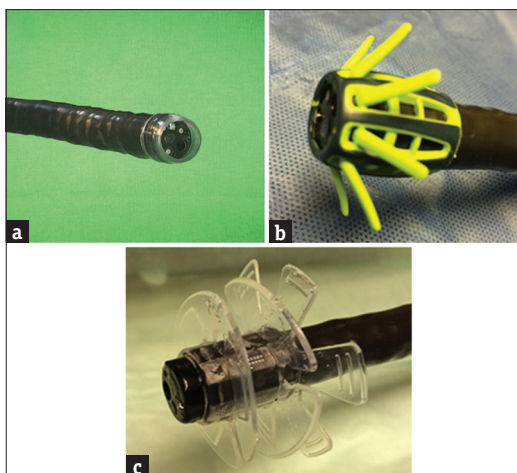
	Fuccio <i>et al.</i> [21]	Zhang <i>et al.</i> [19]	Chen <i>et al.</i> [22]	Shi <i>et al.</i> [20]
Number of RCT (patients)	17 (10350)	40 (13737)	5 (2229)	29 (11464)
ADR, WE versus WI	OR: 1.31 (95% CrI: 1.12-1.55)	OR: 1.3 (95% CrI: 1.0-1.6)	RR: 1.18 (95% CI: 1.05-1.32)	RR: 1.2 (95% CrI: 1.1-1.3)
Right colon ADR, WE versus WI	OR: 1.36 (95% CrI: 1.10-1.70)	NA	RR: 1.31 (95% CI: 1.07-1.61)	NA
ADR, WE versus AI	OR: 1.40 (95% CrI: 1.22-1.62)	OR: 1.4 (95% CrI: 1.2-1.7)	NA	RR: 1.3 (95% CrI: 1.1-1.4)
ADR, WE versus CO <sub>2</sub>	OR: 1.48 (95% CrI: 1.15-1.86)	OR: 1.3 (95% CrI: 1.0-1.8)	NA	RR: 1.2 (95% CrI: 1.1-1.5)

ADR: Adenoma detection rate, AI: Air insufflation, CI: Confidence interval, CO<sub>2</sub>: Carbon dioxide, CrI: Credible interval, NA: Not available, OR: Odds ratio, RCT: Randomized controlled trial, RR: Risk ratio, WE: Water exchange, WI: Water immersion



folds. Based on a network meta-analysis of all available distal attachment devices, add-on devices resulted in the modest improvement in ADR. The increase, however, occurred only in low performing endoscopists [27]. The network meta-analysis included 16,103 patients in 25 two-arm randomized controlled trials (RCTs). The trials compared distal attachment devices, including cap, Endocuff, and EndoRings with standard colonoscopy. Overall, distal attachment devices increased ADR compared with standard colonoscopy (39.3% vs. 35.1%; RR, 1.13; 95% CI, 1.03–1.23; low-quality evidence), with potential absolute increases in ADR to 11.3% for low-performing endoscopists (baseline ADR, 10%) and to 45.2% for high-performing endoscopists (baseline ADR, 40%). Low-quality evidence showed Endocuff increased ADR compared with standard colonoscopy (40.4% vs. 34.6%; RR, 1.21; 95% CI, 1.03–1.41;  $P = 0.02$ ), with increases in ADR to 12% for low-performing endoscopists and to 48% for high-performing endoscopists. On the other hand, very low-quality evidence showed the use of EndoRings (RR, 1.70; 95% CI, 0.86–3.36) or caps (RR, 1.07; 95% CI, 0.96–1.19) compared with standard colonoscopy for increasing ADR [27]. The benefit between different distal attachment devices was uncertain due to very low-quality evidence.

A different report showed contradictory data. Endocuff was shown to benefit only colonoscopists with low-to-moderate ADR compared with standard colonoscopy in a meta-analysis of 12 RCTs (Endocuff,  $n = 4225$ ; standard colonoscopy,  $n = 4151$ ) [28]. ADR was significantly increased with Endocuff versus standard colonoscopy (41.3% vs. 34.2%; RR, 1.20, 95% CI, 1.06–1.36;  $P = 0.003$ ), especially for operators with low-to-moderate ADR ( $<35\%$ ): RR, 1.51, 95% CI, 1.35–1.69;  $P < 0.001$ ), but not for operators with high ADR ( $>45\%$ ): RR = 1.01, 95% CI, 0.93–1.09;  $P = 0.87$ ). The authors concluded that the use of Endocuff may be considered by operators with low-to-moderate ADR. Adverse events associated with Endocuff are rare and limited to mild mucosal erosion (4.0%; 95% CI, 2.0%–8.0%) [28]. Procedure



**Figure 3:** Add-on devices mechanically enhance colonoscopy accessory. (a) Short cap. (b) Endocuff. (c) EndoRings

Note: (b)(c) reproduced from "Gastro-intestinal Endoscopy - Clinical Challenges and Technical Achievements," by Kurniawan N and Keuchel M, 2017, Comput Struct Biotechnol J, 15:168-179. CC BY

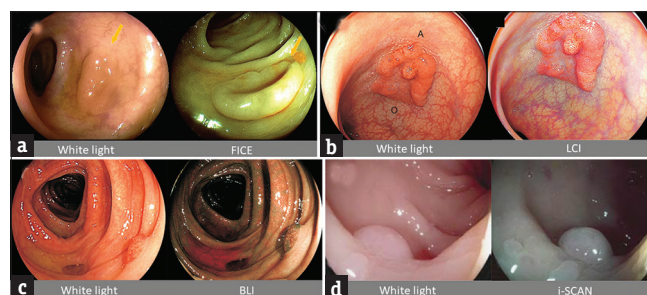
time and cecal intubation rates are similar to those of standard colonoscopy.

Although add-on devices incur a relatively low cost compared with newer scopes, it is still an important issue that could influence their widespread use. It has been shown that the financial recession reduced the use of expensive diagnostic modalities [29].

## ELECTRONIC CHROMOENDOSCOPY

Electronic chromoendoscopy facilitates the visualization of the capillary pattern and surface of the mucosa, thus improving the detection and characterization of polyps and especially nonpolypoid colorectal neoplasms [30-32]. Electronic chromoendoscopy included NBI, Fujinon intelligent chromoendoscopy, i-SCAN, blue-laser imaging, and linked-color imaging [Figure 4] [33,34]. They have been applied to enhance the detection of adenoma. However, the impact of electronic chromoendoscopy on ADR was variable [35]. A meta-analysis with 3507 patients from 7 eligible tandem RCTs examined the adenoma miss rate of electronic chromoendoscopy compared with white-light endoscopy [35]. The pooled adenoma miss rate (17.9% vs. 21%; OR, 0.72, 95% CI, 0.67–1.11;  $P = 0.13$ ) and ADR (OR, 1.02, 95% CI, 0.88–1.19;  $P = 0.78$ ) for electronic chromoendoscopy were not different than those for white-light endoscopy. The pooled adenoma miss rate was statistically significant (OR, 0.60, 95% CI, 0.37–0.98;  $P = 0.04$ ) [35] when only NBI, blue-laser imaging, and linked-color imaging were included.

NBI was the most commonly used electronic chromoendoscopy. The second-generation NBI provides a two-fold brighter image than the previous system, yielding promising ADR results [Figure 5]. A meta-analysis of data from 11 RCTs confirmed that NBI, especially second-generation, may be more effective at detection of adenomas than white-light endoscopy when bowel preparation is optimal [36]. Adenomas were detected in 1011/2239 (45.2%) participants examined by NBI compared with 952/2251 (42.3%) participants examined by



**Figure 4:** Electronic chromoendoscopy facilitates the visualization of the capillary pattern and surface of the mucosa. (a) Fujinon intelligent chromoendoscopy in colonoscopy (Fujinon intelligent chromoendoscopy-filter 4). (b) Linked-color imaging. (c) blue-laser imaging. (d) i-SCAN

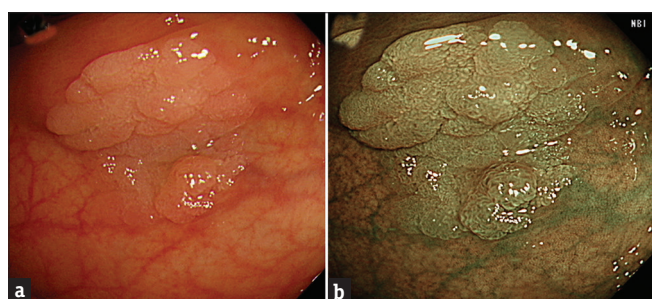
Note: (b)(c) reproduced from "Blue laser imaging, blue light imaging, and linked color imaging for the detection and characterization of colorectal tumors," by Yoshida N, Dohi O, Inoue K, Yasuda R, Murakami T, Hirose R, et al., 2019, Gut Liver; 13:140-8. CC BY-NC 4.0.

(d) reproduced from "High-definition colonoscopy with i-Scan: better diagnosis for small polyps and flat adenomas," by Testoni PA, Notaristefano C, Vailati C, Di Leo M, Viale E, 2012, World J Gastroenterol; 18:5231-9. CC BY-NC 4.0.

**Table 2: Summary of the impact of the endoscopic techniques**

Compared with SC	ADR	Cost	Procedure time	Benefited subgroup	
Low-cost interventions	Overall [11]	OR: 1.29 (95% CI: 1.17-1.43)	+	+/++	NA
	Water exchange [21]	OR: 1.40 (95% CrI: 1.22-1.62)		+	
	Second observation [16]	OR: 1.34 (95% CI: 1.13-1.59)		++	
Add-on devices	Overall [11]	OR: 1.18 (95% CI: 1.07-1.29)	++	-	Low-performing endoscopists [11]
	Endocuff [27]	RR: 1.21 (95% CI: 1.03-1.41)			
	EndoRings [27]	RR: 1.70 (95% CI: 0.86-3.36)			
	Caps [27]	RR: 1.07 (95% CI: 0.96-1.19)			
Enhanced imaging techniques	Overall [11]	OR: 1.21 (95% CI: 1.09-1.35)	NC	NC	NA
	Electronic chromoendoscopy [35]	OR: 1.02 (95% CI: 0.88-1.19)			NA
	NBI [36]	OR: 1.14 (95% CI: 1.01-1.29)			2 <sup>nd</sup> -generation NBI and excellent bowel preparation [36]
Newer scopes	Overall [11]	OR: 0.98 (95% CI: 0.79-1.21)	+++	NC	NA

ADR: Adenoma detection rate, CI: Confidence interval, CrI: Credible interval, NA: Not available, NC: No change, NBI: Narrow band imaging, OR: Odds ratio, RR: Risk ratio, (-): Decrease, (+): Increase

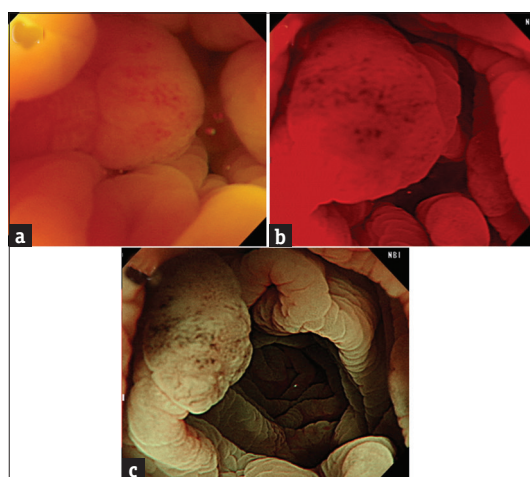


**Figure 5:** The impact of narrow-band imaging systems on the image of a polyp. (a) The white light image of an adenoma. (b) Under narrow-band imaging, the adenoma appeared browner than the background and had a surface pattern of tubular vessels surrounding white structures. The margin of the polyp was also better appreciated

white-light endoscopy (unadjusted OR 1.14; 95% CI, 1.01–1.29;  $P = 0.04$ ). The subgroup analysis suggested that second-generation NBI improved ADR (OR, 1.28; 95% CI, 1.05–1.56;  $P = 0.02$ ), whereas the first-generation NBI did not (OR, 1.06; 95% CI, 0.91–1.24;  $P = 0.48$ ). The improvement in ADR with NBI only maintained statistical significance when bowel preparation was of the best quality (OR, 1.30; 95% CI, 1.04–1.62;  $P = 0.02$ ). However, because fecal material appears brick red under NBI, even a thin film of stool covering the colon would significantly impair mucosal observation [Figure 6].

## CONCLUSION

In summary, low-cost interventions (e.g., WE and second observation), add-on devices, and enhanced imaging techniques are associated with significant improvement in ADR, but newer scopes show no clear benefit compared with high-definition colonoscopy alone [Table 2]. Among those low-cost interventions, WE significantly enhanced overall ADR and right colon ADR, providing higher quality outcome than standard colonoscopy. The ADR benefit of the add-on devices is limited to low performing colonoscopist, while NBI requires excellent bowel preparation. In addition, new endoscopic techniques incur various additional costs, nil for WE, small for tip attachments but large for the newer scopes. In conclusion, colonoscopists participating in the nationwide colorectal cancer screening program in Taiwan should consider applying one or more of the above measures to improve ADR and hopefully reduce



**Figure 6:** The impact of bowel preparation on the images of narrow-band imaging. (a) One adenoma was noted in dirty water. (b) Fecal material appeared brick red under narrow-band imaging and significantly impaired mucosal observation. (c) After water exchange, the visualization of the mucosa has much improved

interval cancers. A comparison of these approaches to determine which is the most cost-effective is warranted.

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## Conflicts of interest

There are no conflicts of interest.

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