

## New endoscopy advances to refine adenoma detection rate for colorectal cancer screening: None is the winner

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### Abstract

Colorectal cancer (CRC) is the third most common

cancer in males and second in females, and globally the fourth cause for cancer death worldwide. Oncological screening of CRC has a major role in the management of the disease and it is mostly performed by colonoscopy. Anyway, effectiveness of endoscopic screening for CRC strictly depends on adequate detection and removal of potentially precancerous lesions, and accuracy of colonoscopy in detection of adenomas is still suboptimal. For this reason, several technological advances have been implemented in order to improve the diagnostic sensitivity of colonoscopy in adenoma detection. Among these: (1) Visual technologies such as chromoendoscopy and narrow band imaging; (2) optical innovation as high definition endoscopy, full-spectrum endoscopy or Third Eye Retroscope; and (3) mechanical advances as Cap assisted colonoscopy, Endocuff, Endoring and G-Eye endoscope. All these technologies advances have been tested over time by clinical studies with mixed results. Which of them is more likely to be successful in the next future?

**Key words:** Colorectal cancer screening; Colonoscopy; Adenoma detection rate; Diagnostic advances

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**Core tip:** Oncological screening of colorectal cancer is mostly performed by colonoscopy and effectiveness of this technique strictly depends on adequate detection and removal of potentially precancerous lesions. Anyway, accuracy of colonoscopy in detection of adenomas is still suboptimal. For this reasons several technological advances have been implemented in order to improve the diagnostic sensitivity of colonoscopy in adenoma detection. Which of them is more likely to be successful in the next future?

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## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in males and second in females, and globally the fourth cause for cancer death worldwide<sup>[1,2]</sup>. Oncological screening of CRC has a major role in the management of the disease, since several randomized controlled trials demonstrated an increase in 5-year survival and a reduction in mortality for healthy subject undergoing surveillance, compared to patients who are diagnosed in the clinical phase of the disease<sup>[3]</sup>. To date several tests have been used in CRC screening, among them fecal occult blood test, fecal DNA test, sigmoidoscopy, colonoscopy and computed tomographic colonography. Anyway colonoscopy has a pivotal role in CRC screening, since it can be used both as primary screening test, both as recall strategy after a positive result of a different test in order to confirm diagnosis and provide removal of polyps. Since effective endoscopic screening for CRC strictly depends on adequate detection and removal of potentially precancerous lesions, over time performance measures and quality indicators have been assessed in order to ensure the quality of the examination and improve patient outcomes<sup>[4-6]</sup>.

The European Society of Gastrointestinal Endoscopy and United European Gastroenterology have recently presented a short list of key performance measures for lower gastrointestinal endoscopy<sup>[7]</sup>. Among these, cecal intubation rates, withdrawal times, quality of bowel preparation and adenoma detection rate (ADR).

ADR is the primary quality indicator for colonoscopy and depends by the performance of the endoscopist. It is defined as the proportion of screening colonoscopies in patients aged 50 years or older detecting at least one adenoma, and it should be ideally at least 25%. A first study in 2010 showed that ADR is an independent predictor of the risk of interval CRC after screening colonoscopy<sup>[8]</sup> and a recent prospective study of individuals who underwent screening colonoscopy within a National Colorectal Cancer Screening Program, showed that increased ADR is associated with reduced risk of interval CRC and death<sup>[9]</sup>. Anyway, despite quality measures, the accuracy of colonoscopy in detection of adenomas is still suboptimal<sup>[10]</sup>. Up to date several technological advances have been implemented in order to improve the diagnostic sensitivity of colonoscopy in adenoma detection.

First of all visual and optical enhancement technologies have been introduced with the aim of improve ADR. In the group of visual enhancement advances, chromoendoscopy and narrow band imaging (NBI) have been test over time. As suggested by a Cochrane review, chromoendoscopy can improve detection of polyps, anyway it is a time-consuming technique and it

is not always feasible in real practice<sup>[11]</sup>. Contrariwise, as showed by several studies, NBI does not improve ADR during colonoscopy<sup>[12,13]</sup>. Among optical innovation, high definition endoscopy (HDE), using high definition monitor and a high resolution charge coupled device with up to a million pixels, allows a better image view compared to standard vision endoscopy (SVE). Anyway studies report conflicting results. A recent meta-analysis comparing high definition vs standard video endoscopy showed, in favor of HDE, an incremental yield of 3.8% (95%CI: 1%-6.7%) for the detection of any polyp, an incremental yield of 3.5% (95%CI: 0.9%-6.1%) for detection of adenomatous polyps and no differences between HDE and SVE in the detection of high-risk adenomas<sup>[14]</sup>.

The full-spectrum endoscopy (FUSE, EndoChoice, GA, United States) is a new technology using a colonoscope equipped with two lateral lenses, in addition to the one on the forward tip, so to increase the maximum field of view up to 330°, compared to the ≤ 170° of standard forward-viewing (SFV) colonoscopy. This allows greater visual field and, at least in theory, greater detection rate of polyps.

A multicenter, randomized back-to-back study showed a significantly higher detection rate of adenomas (69% additional adenomas) and a lower adenoma miss rate with FUSE (7%) respect to SFV colonoscopy (41%) ( $P < 0.0001$ )<sup>[15]</sup>.

Despite this good premise, a randomized controlled trial performed on a large population of patients undergoing colonoscopy following a positive fecal immunochemical test, showed no statistically significant difference in detection rates of adenomas (ADR) and advanced adenomas (defined as adenomas ≥ 10 mm and/or with villous component > 20%, and/or high-grade dysplasia) in a per patient analysis<sup>[16]</sup>.

Another recent randomized back to back study compared adenoma miss rates of full-spectrum endoscopy (FSC) with those of conventional colonoscopy complemented by right-colon re-examination using scope retroflexion (CC/R) performed by endoscopists with documented ADRs > 35%. FSC showed, by a per-lesion analysis, a significantly lower adenoma miss rate compared with CC/R [10.9% (95%CI: 3.8-18.1) vs 33.7% (95%CI: 23.4-44.1)] and a lower advanced adenoma miss rate lower with FSC [4.3% (95%CI: -4.0-12.7) vs 25.9% (95%CI: 9.4-42.5)] showing as FSC outperforms conventional colonoscopy even when performed by experienced endoscopists<sup>[17]</sup>. Therefore, despite its good technical result, so far literature data are conflicting and a definite benefit on ADR has not been yet demonstrated.

One more technological solution is the Third Eye Retroscope (TER; Avantis Medical Systems, Inc), a device that can be inserted through a standard colonoscope's working channel, advanced over the tip and bend to 180 degrees before the withdrawal phase, in order to obtain an additional backward view that increases the visibility of blind areas not fully visible on standard view examination.

Studies performed so far showed a gain in ADR from 13.2% to 23.2%<sup>[18,19]</sup>. Despite a quite gain in adenoma detection, however the procedure is time consuming and presents some disadvantages such as an inferior image quality, a reduced suction capacity of the scope and the necessity of removing the third eye retroscope whenever another device need to be inserted through the working channel.

One additional method to enhance ADR is that to obtain a mechanical improvement of endoscopic view by a mechanical flattening of haustral folds and tip stabilization. In this line, several devices have been introduced to refine efficiency of the standard colonoscopy, such as cap, cuff and rings.

Cap assisted colonoscopy (CAC) is a simple technique utilizing a transparent cap mounted on the tip of a standard colonoscopy, with the aim to obtain folds flattening during withdrawal and preventing the collapse of the mucosa against lenses. This device have been originally used during endoscopic submucosal dissection (ESD) and subsequently tested also for diagnostic colonoscopy in order to enhance visibility of blind areas and improve ADR. A recent meta-analysis performed on 4 studies compared CAC vs standard colonoscopy (SC), showed a higher right ADR (23% vs 17%; OR = 1.49, 95%CI: 1.08-2.05;  $I^2 = 79%$ ;  $P = 0.01$ ), similar to that obtained with TER, and an improved detection rate of flat adenoma (OR = 2.08; 95%CI: 1.35-3.20;  $P < 0.01$ ) for CAC respect to SC<sup>[20]</sup>. Another meta-analysis of 23 RCTs comparing CAC vs SC showed an increase in detection rate of polyps (OR = 1.17,  $P < 0.01$ ), but no statistically significant difference in ADR<sup>[21]</sup>.

One different mechanical solution is Endorings (EndoAid Ltd., Caesarea, Israel), a silicone-rubber device fitted onto the distal end of the colonoscopy and composed by flexible circular rings that allow mechanical stretch of colonic folds during withdrawal and stabilize the tip to the center of the lumen. A recent multicenter, randomized study showed that EndoRings colonoscopy compared with standard colonoscopy allows a lower polyp miss rate (9.1% vs 52.8%;  $P < 0.001$ ) and a significantly lower adenoma miss rate (10.4% vs 48.3%;  $P < 0.001$ )<sup>[22]</sup>.

Similarly to Endorings, Endocuff (Arc Medical, Leeds, United Kingdom) is a plastic mechanical device provided with rows of finger-like projections, which is mounted onto the distal tip of endoscope. During gently insertion of colonoscopy, finger projections collapse back, while during withdrawal they flare out allowing a mechanical grip with flattening of the colonic folds and centering the tip in the lumen. Two RCTs showed that colonoscopy with Endocuff increase by 63% detection of polyps and by 83% detection of adenoma<sup>[23]</sup>, as well as increase significantly ADR (35% vs 21%;  $P < 0.0001$ ) respect to standard colonoscopy<sup>[24]</sup>.

Contrariwise to these results a subsequent RCT performed on a large number of patients, even showing an higher detection of adenomas sized  $< 6$  mm (443 vs 378;  $P = 0.03$ ) and of flat polyps (213 vs 161;  $P =$

0.03), did not found difference in ADR overall between Endocuff and standard colonoscopy<sup>[25]</sup>. Finally, the use of EndoRings and Endocuff is safe since no major adverse events have been registered so far, while minor drawbacks are the possibility of device detachment from the colonoscopy and risk of slight mucosal lacerations.

One of the latest mechanical advances is G-EYE (Smart Medical Systems Ltd). The G-EYE endoscope employs a permanently-integrated balloon at the tip of the standard endoscope, which is moderately inflated at a selected partial pressure during withdrawal, with the aim to straighten colonic folds, centering the tip and enhancing endoscopic visibility. This technique has been assessed in a randomized tandem study showing that G-EYE colonoscopy increased ADR by 81% ( $P < 0.001$ ) and lowered adenoma miss rate (7.5% vs 44.7%;  $P = 0.0002$ ) compared with standard colonoscopy, without significant adverse events<sup>[26]</sup>.

## DISCUSSION

Oncological screening have a key role in the prevention of CRC and strong evidences from literature clearly demonstrated an increase in 5-year survival and a reduction in mortality for healthy subject undergoing surveillance. Although colonoscopy is the gold standard for CRC screening, its accuracy is still suboptimal and a significant number of adenomas are still missed during examination, mostly due to inherent limitations of the technique that does not allow a full visualization of hidden points especially the ones behind colonic folds and flexures.

Today one of the most important challenges is that to increase the quality of the endoscopic technique, with the aim to enhance ADR and consequently the effectiveness of oncological screening. On this line, many innovations have been developed with promising results. Between these, HDE showed excellent results in terms of image definition and will probably replace over time the standard definition technology. Similarly, the FUSE showed a spectacular 330° field of view, but recent evidences proved no difference in ADR and it is unlikely that this technology will be further developed in the future. The use third eye retroscope showed a gain in ADR, but this device is burdened by an inferior quality of image and the procedure is often time consuming and not always comfortable.

Mechanical advances such as CAP assisted colonoscopy, EndoRings and Endocuff showed promising result in terms of ADR. In addition these solutions are simple to use, economical and safe. Anyway, before recommending a widespread use, further randomized controlled trials are needed in order to better assess performance of these devices. Finally, G-EYE endoscope has been recently introduced and needs further studies.

In conclusion, great technological advances have been made so far, but none of these innovations have been proven to be so effective to be strongly recommended right now in clinical practice worldwide.

Currently existing devices require further assessment, and at the same time new technologies need to be developed.

Waiting for that, we recommend the use of high definition image systems ensuring, at the same time, adherence to quality measures for lower endoscopy, including high cecal intubation rates, withdrawal times of 6 min or longer and optimal quality of bowel preparation.

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