

Detection and characterisation of colorectal polyps

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Abstract

Colonoscopy remains the gold standard investigation for the detection and resection of premalignant colorectal polyps.

The introduction to the thesis (chapter 1) reviews the literature on detection and characterisation of colorectal polyps at colonoscopy. It explores the biological significance of small polyps and describes how advanced technology and new techniques could help to reduce polyp miss rates and accurately characterise polyps in vivo.

The first study in the thesis (chapter 2) examines the likely proportion of missed colorectal polyps at bowel cancer screening colonoscopy informing subsequent studies (chapter 3-5) that explore ways to improve polyp detection: a modification to the standard examination technique at flexible sigmoidoscopy is assessed as is the use of a novel wide – angled colonoscope and the use of a specially designed disposable distal attachment (Endocuff).

The adenoma detection rate (ADR) has long been proposed as the optimal metric for assessing quality of detection at colonoscopy but in chapter 6 a novel ‘‘efficiency marker’’ is proposed as a potentially more useful performance measure to compare the efficiency of novel colonoscopy interventions.

In chapter 7 an image evaluation study explores whether a well validated polyp classification system (NICE), using narrow band imaging of polyps is equally applicable when a novel blue laser imaging (BLI) is used. Two further studies address technical aspects of optical diagnosis implementation in routine clinical practice. A retrospective study (chapter 8) documents the colonic distribution of sessile serrated polyps and in particular their prevalence in recto - sigmoid colon where differentiation from simple hyperplastic polyps may be difficult on optical grounds whilst chapter 9 assess the learning curve of optical diagnosis in trainees

showing that the application of cumulative summation monitoring could be used to quality assure performance in optical diagnosis.

The final chapter (10) discusses the results from the thesis and explores future directions and characterisation of colorectal polyps.

Dedicated to my family without whom none of this would have been possible

Preface

This thesis represents original work carried out by the author at the Wolfson Endoscopy and Academic Institute, St Mark's Hospital. The work has not been presented in any other form to any other institution. Where the data has been used in manuscripts, it is appropriately acknowledged.

The studies and reviews were carried out under the supervision of Prof Brian P Saunders (Imperial College London and St Mark's Hospital), Prof Paris Tekkis (Imperial College London and Royal Marsden Hospital) and Dr Ana Wilson (Imperial College London and St Mark's Hospital).

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Chapter 1

Introduction

1.1 Background

Colonoscopy is the current gold standard for detecting and removing dysplastic colonic polyps, precursors to colorectal cancer (CRC), and as such has been adopted as a primary screening tool for CRC in many countries.

Colorectal cancer is one of the commonest causes of significant morbidity and mortality in the western world. It is the second most common cause of cancer related mortality in Europe and the 4th most common cause worldwide (1).

In the United Kingdom, more than 40000 new patients are diagnosed as having the disease and around 16000 deaths occur due to the disease each year (2). CRC is the UK's third most common cancer in men and women costing the UK approximately £1.6bn. According to Cancer Research UK, it affected 86 per 100,000 males compared to 57 per 100,000 females in 2018 (3). Since the early 1990s, CRC incidence rates have remained stable in the UK. Rates in females remained stable and in males the rates have decreased by about 3% (4). The use of colonoscopy as a screening and therapeutic tool and the emerging literature on missed cancers at colonoscopy has driven improvements in quality and efficiency of the procedure. This thesis addresses the ways that advanced technology could be used to improve detection and characterisation of colorectal polyps during colonoscopy.

1.2 Role of colonoscopy in colorectal cancer prevention

In England, the NHS bowel cancer screening programme began in 2006. It now offers Faecal Immunochemical Test (FIT) screening every two years to the public aged 60-75 years, followed by a colonoscopy for those who meet the FIT threshold. This has exerted additional pressure on the colonoscopy services in the NHS. Currently, over 650000 colonoscopies are performed each year(5) with numbers of procedures increasing annually.

Colonoscopy offers a simultaneous diagnostic and therapeutic capability of detection and resection of premalignant polyps (adenomas and sessile serrated lesions), which in turn provides the opportunity to change the natural history of CRC by reducing the risk of CRC development. Endoscopic polypectomy is effective in reducing CRC incidence and mortality(6). Mortality from CRC among patients with adenomas removed was compared with the expected incidence from CRC in the general population as estimated from the SEER (Surveillance Epidemiology and End Results) and showed a 53% reduction in mortality and 76-90% reduction in detection of CRC(7). A recent meta analysis, which analysed 11 observational studies with a total of almost 1.5 million individuals showed that colonoscopy was associated with a 61% reduction in CRC incidence (RR: 0.39;95% CI: 0.26-0.60, $I^2=93.6\%$) and a 61% reduction in CRC mortality (RR: 0.39;95% CI: 0.35-0.43; $I^2=12\%$) (8).

However higher than expected rates of post colonoscopy CRC (PCCRC) demonstrate the fallibility of current techniques of colonic assessment during a routine colonoscopy. PCCRC is defined as cancers detected during a colonoscopy within 3 years of a false negative colonoscopy. PCCRC Evidence suggests that up to 700 patients are diagnosed as having PCCRC each year in the English NHS(9) and is inversely related to adenoma detection rate (ADR) which is defined as the proportion of colonoscopies where one or more adenomas is detected. (10, 11).

1.3 Colorectal cancer and polyp development

1.3.1 Colorectal cancer pathways

1.3.1.1 *Chromosomal instability pathway*

This pathway is the most common sequence of colorectal carcinogenesis arising from adenoma precursors. It is estimated that around 70% of CRCs arise via the CIN pathway(12). It involves a progression from normal epithelium to low grade dysplastic adenomas (Figure 1) to larger lesions with high grade dysplasia and evolves to an invasive cancer as a result of mutations in a number of genes, including APC, KRAS/BRAF, TP53 and SMAD4(13).

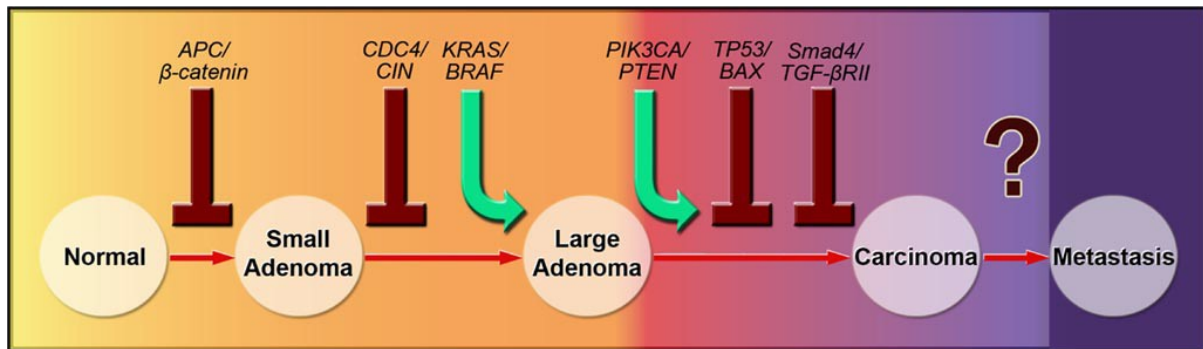


Figure 1. Genetic alterations associated with tumour carcinogenesis. Adapted from Jones S et al(13).

1.3.1.2 *Microsatellite instability pathway*

The second major CRC pathway which is responsible for around 15% of CRC is the MSI pathway. Of these tumours, about 20% have a hereditary cause and arise in patients with a germ line mutation in one of the mismatch repair genes, the Lynch syndrome(14). The remaining 80% of MSI CRC arise due to hypermethylation of the promoter of the mismatch repair (MMR) gene(15). The pathophysiology of MMR dysfunction and subsequent cancer risk account for tumours with a sporadic cause of MMR dysfunction. Neoplastic transformation via the hereditary MSI pathway is said to be faster compared with the CIN pathway, resulting in CRC within approximately 3-5 years(16).

1.3.1.3 *Serrated neoplasia pathway (SNP)*

It is suggested that sessile serrated adenomas/polyps (SSA/Ps) are the main precursors of CRC developing via the serrated pathway and responsible for 15-30% of CRCs(14, 17). The existence of SNP was first described about 15 years ago and is characterised by hypermethylation and subsequent silencing of tumour suppressor genes and a mutation in the BRAF oncogene(14).

1.3.2 Evolution of polyps

Adenomas are typically composed of abnormal, dysplastic crypts, structures which are morphologically similar to the non-neoplastic part of the healthy colon. The majority of the abnormal crypt population is produced around the same time, near the onset of tumour formation, and then this initial period of growth is followed by stasis. A stem cell population within adenomas suggest that new growth of intra tumour clones occurs infrequently(18).

The relative timing of the birth of founder cells (Fcell) gives rise to various tumour cell population is shown in figure 2. All somatic mutations present in clonal fashion in an adenoma must have been present in its founder cells. These mutations accumulated during the life span of founder cells and as tumour progress, they accumulate additional mutations which are attached to founder cells of subsequent neoplastic states(19). This mathematical model explains the average time between the transformation of small adenomas to cancer is around 17 years.

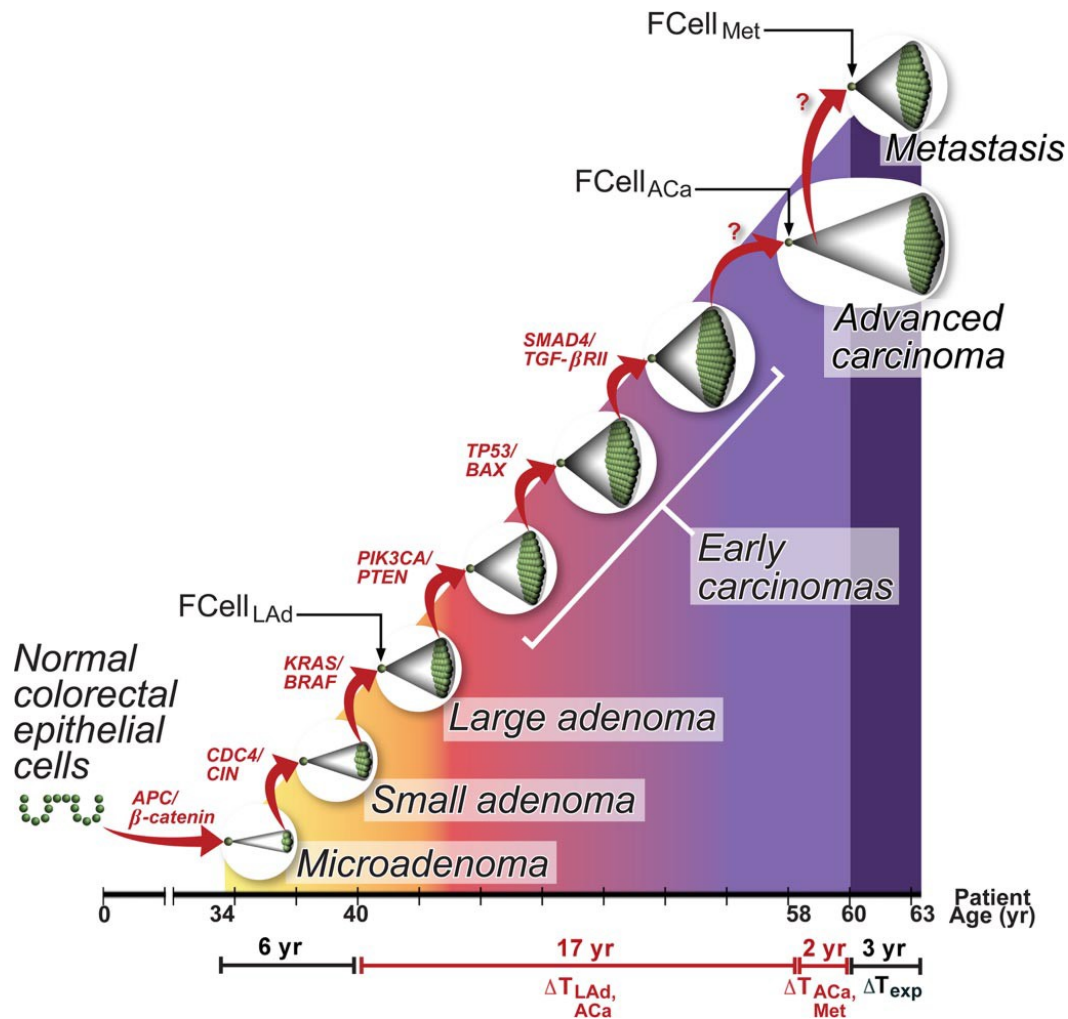


Figure 2. Evolution and growth of cancer from microadenoma. Adapted from Jones et al(19).

1.3.2.1 Polyp growth

Longitudinal studies have found that fewer than 10% of adenomas become malignant within 10 year of first detection(20). Estimates of adenoma growth rates based on longitudinal endoscopic and CTC studies suggest that most adenomas remain relatively static in size for many years with a substantial proportion of smaller polyps even regressing over time(21-23).

A CTC surveillance study of 95 small polyps demonstrated a volumetric growth of 30% or more, while 38% of polyps remained stable, 13% had a volume reduction of 30% or more and 14% appeared to be completely regress after a 3-year surveillance interval(24).

Mizuno and colleagues studied the natural history of 207 diminutive colorectal polyps over a median of 7.5 years(25). The mean change in linear size was 0.6mm and the mean percentage of change varied between -10% to 10%, as seen for 170 polyps (84%), whereas 28 polyps (14%) showed a percentage size change of >10%. Pickhardt et al. reported that small, advanced adenomas grow more rapidly than non-advanced adenomas(26). These studies highlight that polyps <10mm tend to grow at a slower pace.

1.3.3 Missed polyps

Most PCCRC are thought arise from missed polyps during index examination. Each endoscopist's ADR has been shown to be inversely associated with the risk of PCCRC and cancer related mortality(10). Furthermore, Corley and colleagues examined 314,872 colonoscopies and concluded that for each 1% increase in ADR, the risk of interval or PCCRC decrease by 3%(11). Rex and colleagues performed tandem colonoscopies on 183 patients and reported a miss rates of 27% ($\leq$ 5mm adenomas), 13% (6-9mm adenomas) and 6% for adenomas > 1cm(27). A systematic review and meta analysis of tandem studies established a pooled polyp miss rate of 22% (28). In this review the miss rate for polyps >1cm was 2.1%

1.4 Quality of Colonoscopy

It is clear that a complete, high quality colonoscopy examination is not just achieved by inserting the colonoscope to the caecal pole. Rather it depends on many factors including quality of bowel preparation, ability to visualise whole colonic mucosal surface, image quality, interpretation and recognition of abnormal findings and endoscopists examination technique. Figure 3 illustrates the interplay of those factors in determining the quality of a colonoscopic examination in cancer detection and prevention.

1.5 Factors influence the quality of colonoscopy and polyp detection

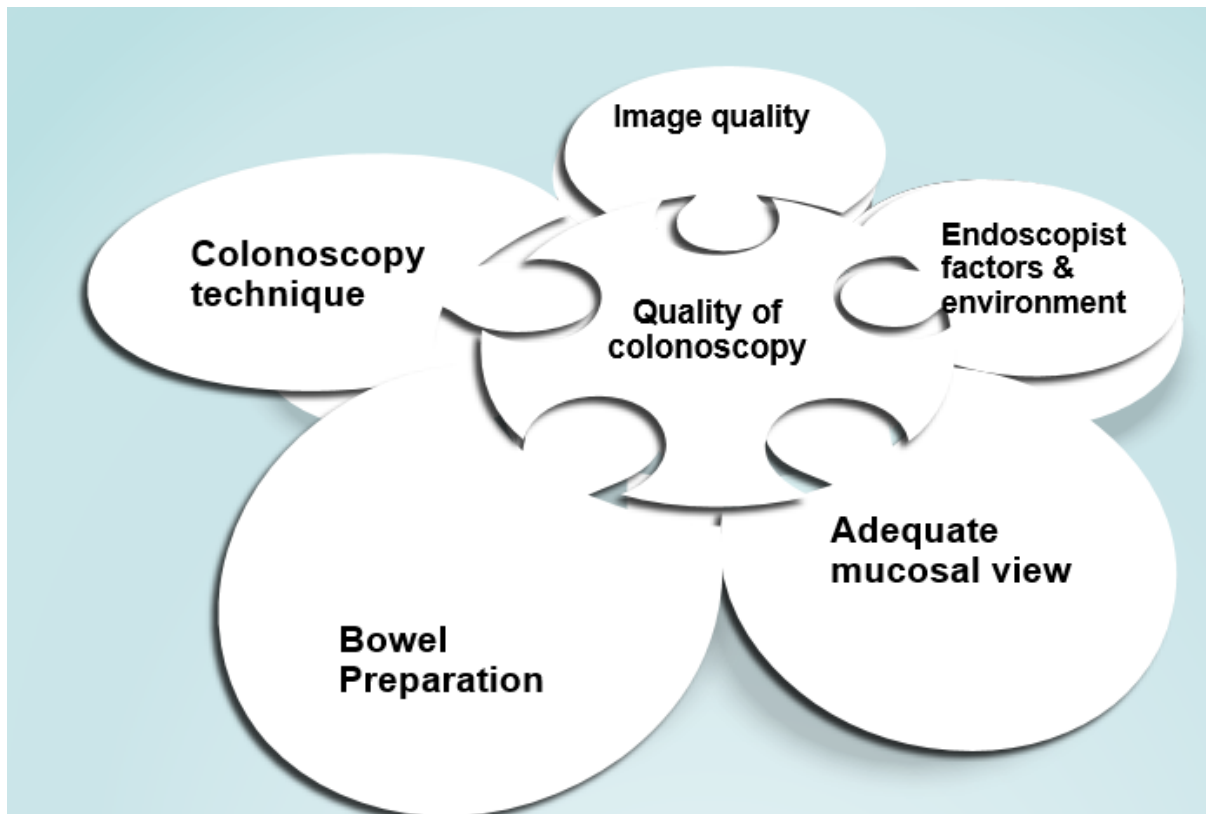


Figure 3. Factors influence the quality of colonoscopy

1.5.1 Bowel preparation

Effective bowel cleansing is fundamental for a high-quality colonoscopy. Good or optimal bowel preparation allows completion of examination to the caecum and detection, characterisation, and the subsequent resection of neoplastic polyps. Poor bowel cleansing is associated with incomplete, prolonged procedures which lead to failure to detect significant pathology(29-31). The quality of bowel preparation should be recorded and included in the colonoscopy report. Many clinicians use a standardised 4-point scale

(excellent, good, fair, and poor) to describe the level of bowel cleansing. Many endoscopists shorten the interval between examinations or repeat the colonoscopy if bowel preparation is considered inadequate(32, 33). A recent systematic review and meta analysis of 21 studies showed no difference in ADR for excellent, good and fair bowel preparation, but ADR

decreased with poor and insufficient preparation (poor: OR 0.63, CI 0.44-0.91, $P < 0.015$; insufficient: OR 0.43, CI 0.33-0.56 , $p, 0.001$)(34).

Data from national endoscopy database highlighted that an adequate preparation resulted in an improved ADR for adenomas of any size (OR 1.21, 95CI, 1.16-1.25) when compared to inadequate preparation(29). Flat and SSA/Ps in proximal colon are most likely to be detected when the preparation is optimal. A single centre study enrolled 749 screening patients reported a significantly smaller proportion of SSA/Ps and flat lesions with intermediate quality preparation than high quality preparation (4.6% vs 12%, OR:0.19, 95% CI, 0.05-0.81)(35).

Endoscopists should strive to achieve optimal level of preparation in majority of patients to ensure all significant pathological lesions are detected and dealt with.

1.5.2 Techniques to enhance colonic mucosal visualisation

1.5.2.1 *Colonoscopy technique*

Adequate luminal distension is key to achieving complete visualisation of the mucosa. This can be partly achieved by insufflation of air or CO₂, but air may escape to less dependent parts of the colon leading to excessive insufflation and resulting in abdominal discomfort during or after the procedure. Discomfort due to over insufflation of can result in incomplete colonoscopy from poor tolerance of the procedure and technically more difficult insertions due to bowel elongation, particularly in patients with redundant colons. Redundancy and excessive looping is commonly encountered in patients with central obesity and chronic constipation (36). To overcome this difficulty, water infusion is used to minimise discomfort and to improve completion rate of colonoscopy. Water assisted colonoscopy (WAC) is a technique that is increasing in popularity. When the colon is filled with water, the sigmoid colon is weighted down and straightened decreasing the acuity of tight angles. Furthermore, unlike air or CO₂ it shortens the colon rather than distending it. Water acts as a lubricant to the scope and eases the

passage of the colonoscope(37). Several studies have shown a reduction in sedation requirements when WAC was performed compared to the standard air/CO₂ method(38, 39). A recent meta analysis of 13 studies involving 7056 patients confirmed the observation that WAC was associated with significantly lower patient pain score (weighted mean difference - 1.99, 95% CI;-2.68, -1.30, p<0.00001) and lower request for on demand sedation (RR=0.58,95% CI;0.44-0.77, p=0.0002) when compared to air insufflation. In addition, WAC was associated with high ADR (RR=1.28,95% CI;1.18, -1.38, p,0.0001). WAC may improve ADR through several proposed mechanisms: infusion of water aids to clear the luminal debris and residue, lack of distension with water allows polyps to float and not be flattened against the colonic wall making them more visible and water has a magnifying effect and that may enhance polyp detection(40).

1.5.2.2 *Dynamic position changes (DPC)*

Position changes have been shown to increase visualisation at virtual colonoscopy(41). A video analysis of 14 patients who were attending routine colonoscopy, showed multiple position changes during colonoscope withdrawal improved luminal distension between the hepatic flexure and sigmoid descending junction(42). This prompted authors of this study to embark on a randomised crossover trial to validate the effect of DPC on ADR. It showed a 11% increase in ADR with DPC when compared to left lateral position alone(43). A recent meta analysis and systematic review of 5 randomised controlled trials showed that dynamic position changes were associated with high ADR when compared to static left lateral position (OR 1.34;95% CI 0.88-1.73)(44).

1.5.2.3 *Withdrawal technique*

Meticulous examination of the colonic mucosa on withdrawal is essential for a quality examination. Withdrawal time (WT) of >6min has been linked to higher ADR(45). Therefore, this is endorsed as a key performance indicator of the quality of withdrawal technique by

national and international societies(5). An increased WT provides more time to distend the colon, aspirate fluid residues, and examine the proximal side of haustral folds(46).

Other manoeuvres such as retro flexion in the right colon and routine use of anti-spasmodic agents produced conflicting results. Based on available data, the routine use of those manoeuvres is not recommended at present(47-49).

1.5.3 High definition colonoscope and image quality

High definition (HD) colonoscopes producing clearer images of the mucosa may help to improve PDR. However, a retrospective cohort comparative study of a standard definition colonoscope with a HD colonoscope in 9000 procedures failed to show any clear benefits in PDR (43% and 46%, $p<0.42$) or ADR (24.9% and 24.2%, $p=0.82$)(50). Five other studies have compared ADR between SD and HD colonoscopy and have failed to show any differences(51-55).

1.5.4 Other technologies to visualise proximal side of folds.

Other technologies such as the third eye retroscope, FUSE and G-eye balloon scope have showed promising results. The third eye retroscope was evaluated in 345 patients in a tandem study compared with SD colonoscopy and showed a superior ADR (net improvement of 23%) (56). The G-eye Balloon scope was evaluated in two tandem studies(57, 58) showing lower polyp (7% vs 41%, $p=0.0002$) and adenoma miss rate (7.5% vs 44.7%, $p=0.0002$) when compared to SC.

1.5.5 Disposable distal attachments

The relative simplicity and single use application of distal attachments make their use for enhanced polyp detection compelling and easily applicable compared to some other technologies such as third eye retroscope that blocks the accessory channel.

1.5.5.1 *Endocuff and Endocuff vision TM*

Endocuff-vision (EV) is mounted at the tip of the scope and held in place by friction with a unique dynamic shape and one row of arms compared to the Endocuff-original (Figure 4) that had two. The core is made of polypropylene and the ‘arms’ are made of a thermoplastic elastomer. EV comes in four colour coded sizes (purple, blue, green and orange) to fit a range of paediatric and adult colonoscopes. The EV features a single proximal row of eight backwards pointing ‘arms’ at intervals around the device circumference with the following dimensions in different cuff sizes (length of 23.8mm x diameters of 16.1/16.7/17.2/18.5mm with the ‘arms’ folded back and 39.07/39.07/39.07/39.66mm with ‘arms’ opened out).



Figure 4. Endocuff Vision and Endocuff-original EV (one proximal row of ‘arms’), Endocuff (one proximal and one distal row of ‘arms’).

The EV is placed snugly around the colonoscope tip prior to insertion and does not project beyond the tip of the scope, providing an unrestricted view. The soft, elastic ‘arms’ are fold

back (recoiled) towards the scope shaft during insertion but evert during withdrawal to hold colon folds away from the field of view. This helps anchor the scope tip against the bowel wall, resulting in a stable position of the colonoscope tip, which is particularly useful when removing polyps in difficult positions(59). EV has the following contraindications: i) known colonic strictures, and ii) active inflammatory disorders such as acute infective colitis, active colonic Crohn's disease, Ulcerative Colitis, and acute diverticulitis. The EV features a hinge at the base of each 'arm' that acts as a pivot point, which thins towards its tip so that it is relatively more flexible at the tip than at its base. Thus, forward motion through large diameter bowel offers little resistance because the 'arms' flex at the very tip in preference to arm rotation around the hinge. The overall force applied to the bowel wall during forward motion is a negligible (0.06 – 0.08 Newtons). On the other hand, during withdrawal, a rotation around the hinge has been added to permit flexion of the 'arms. Each 'arm', furthermore, abuts the shaft of the device allowing rotation of 60 degrees forward motion from its resting position (30 degrees forward from the horizontal). These unique features exert a tip grip force of up to 1.23 Newtons during withdrawal or when straightening loops, 15 times more than the force required to intubate.

Several studies showed that the Endocuff helps to improve ADR and SSA/Ps detection rates by improve visualisation of colonic mucosa on withdrawal (60-63). Two early studies showed no difference in ADR between Endocuff assisted colonoscopy (EAC) and Standard colonoscopy (SC)(64, 65). However, a recent meta analysis of 9 studies involving 3027 patients comparing EAC with SC showed that ADR in the EAC arm was significantly higher (RR=1.18,95% CI 1.05-1.32, p=0.005)(66).

1.5.5.2 *Plastic Cap (Distal Attachment)*

Transparent caps attached to the distal end of the colonoscope have been suggested to help flatten folds to improve visualisation of proximal side of colonic folds. Even though the Cap helps to provide a platform and give tamponade to bleeding vessels during large polyp

resections, studies assessing the cap to improve ADR show conflicting results. One of the largest RCT's compared Cap assisted colonoscopy (CAC) with SC by 10 experienced endoscopists in 1113 patients and showed no difference in ADR between CAC and SC (42% and 40%, $p=0.452$). A recent meta analysis however compared the performance of CAC with SC for ADR(67) and 7 RCTs were included in the analysis showing a higher ADR when the cap was used compared to SC (OR1.18, 95% CI, 1.03-1.33).

1.5.5.3 *Endorings*

The device is made of silicone rubber and is fitted to the distal tip of the colonoscope. There are two (three in the first design) flexible circular rings that engage and stretch the colonic fold during withdrawal to improve visualisation (Figure 5). In a multicentre, randomised tandem evaluation of 116 patients Endorings assisted colonoscopy showed significantly lower adenoma (10.4% and 48.3%, $p<0.001$) and polyp miss rate (9.1% and 52.8%, $p<0.001$) when compared to SC(68). Rex and colleagues- performed a RCT involving Endocuff, Endorings, FUSE and SC with a total number of 1188 patients. ADR was significantly higher with Endocuff, Endorings and SC compared to FUSE ($p=0.006$).



Figure 5. Endorings

1.5.6 Electronic chromoendoscopy and polyp detection

Electronic chromoendoscopy (EC) includes endoscopic imaging technologies which provide detailed contrast enhancement of the mucosal surface and blood vessels. They provide an alternative to conventional chromoendoscopy using indigo carmine or methylene blue dye. EC are equipment-based image enhancing technologies which improve mucosal visualisation of surface and vascular structures through the use of optical filters or software driven post image processing(69, 70). EC technologies include narrow-band imaging (NBI) (Olympus Medical Co, Tokyo, Japan), flexible spectral imaging colour enhancement (FICE) (Fujinon, Fujifilm Co, Saitama, Japan), i-Scan (Pentax Endoscopy, Tokyo, Japan) and Blue Laser Imaging (BLI) (Fujinon, Fujifilm Co, Saitama, Japan). NBI is the most extensively evaluated EC technique in patients undergoing screening or surveillance colonoscopy.

1.5.6.1 NBI

NBI is the most extensively evaluated EC modality in terms of adenoma detection. Multiple randomised controlled trials have shown no significant difference in adenoma detection when comparing NBI assisted visualisation to standard white light inspection (WLI). East and colleagues randomised 214 patients to examination with NBI or WLI.⁹ They showed there was no significant difference in ADR between NBI and WLI (OR 1.4, 95% CI 1.52-4.63, $p=0.26$). However detection of flat adenomas were significantly better with NBI (CR1.92, 95% CI 1.07-3.44, $p=0.003$)(71). Similar results were highlighted in the study performed by Ikematsu and colleagues(72). This was a multicentre, tandem study that randomised 813 patients to undergo either NBI followed by WLI or WLI followed by NBI examinations. They detected no significant difference in ADR (42.3% for NBI and 42.5% for WLI).

Meta-analyses comparing WLI and NBI for detection of adenomas are summarised in Table 1(73-78). Overall, the superiority of NBI over WLI for adenoma detection is not universal and not convincing. One meta-analysis showed that NBI performed better in detecting flat adenomas (RR 1.96, 95% CI 1.09-3.52), $p=0.02$)(73).

Table 1. Meta analyses of NBI and WL

Author	Year of publication	No of studies	No of patients	ADR
Jin et al ⁷¹	2011	08	3049	RR 1.09(95% CI,1.00-1.19)
Dinesen et al ⁷²	2012	07	2936	RR 1.06(95% CI,0.92-1.16)
Nagorni et al ⁷³	2012	08	3673	RR 0.94(95% CI, 0.87-1.02)
Pasha et al ⁷⁴	2012	09	3059	OR 1.01(95% CI,0.74-1.37)
Omata et al ⁷⁵	2014	14	5074	RR 1.03(95%CI,0.96-1.11)
Li et al ⁷⁸	2019	14	5600	OR 1.29 (95% CI, 1.04-1.58)

A recent study comparing new generation NBI (Olympus Exera HQ190) and HD WLI in a randomized trial with tandem colonoscopy showed encouraging results for NBI(79) . ADR

were significantly better in the NBI group when compared to WLI (48.3% and 34.4%, $p=0.01$). Similarly, the polyp detection rate was better with NBI (61.1% and 48.3%, $p=0.02$).

SSA/Ps can be easily missed at colonoscopy due to their subtle appearance (pale colour, poorly defined edges and the presence of mucus on the surface)(80). Therefore, endoscopists need to spend additional time to carefully examine the mucosa for SSA/Ps especially in the right colon.

NBI has the potential to improve the detection of these subtle lesions. Recently Rex and colleagues performed a randomized controlled trial involving 804 patients to determine the impact of new generation NBI (Olympus 190 series) to detect SSA/P's(81). More SSA/P's, proximal to the sigmoid colon of any size were detected in NBI group when compared to the WLI group (204 and 158, $p=0.085$), but failed to achieve statistical significance.

1.5.6.2 FICE

FICE is a digital imaging post-processing technique, in which WL endoscopic images from the video processor are altered to display a composite colour-enhanced image in real time. There is limited data available on the use of FICE. Two prospective, randomized, controlled trials compared FICE with WLI and failed to show any improvement in polyp or adenoma detection. Aminalal and colleagues recruited 637 patients into each arm of the study(82) and there was no difference in polyp detection (31.9% with FICE and 27.7% with WLI, $p=0.10$) or ADR (28% each, $p=0.95$). More small polyps ($<10\text{mm}$) were detected with FICE compared to WLI (54.4% and 43.8%, $p=0.008$). A second trial performed by Pohl and colleagues involving 764 patients, did not demonstrate an improvement in adenoma detection with FICE compared to WLI (236 and 271, $p=0.92$)(83). A randomized, tandem study in average risk patients undergoing screening colonoscopy compared WLI either with NBI or FICE(84). Chung and colleagues recruited 1650 subjects (550 in each group) and FICE did not show any incremental increase in ADR when compared with WLI or NBI (25.3%, 24.5%,

$p=0.75$). A meta-analysis conducted by Omata and colleagues, comparing FICE and i-scan showed no benefit over WLI (RR 1.09; 95% CI, 0.97-1.23)(77).

1.5.6.3 *i-Scan*

i-Scan is a software-based digital, post processing image enhancement technology. The studies using i-Scan to enhance adenoma detections show conflicting results. Hoffmann and colleagues highlighted a superior ADR with i-Scan when compared to WLI (38% and 13%; $p<0.0001$)(85). The detection rate for flat adenomas was higher with i-Scan compared to white light (58% vs 23%, $p<0.0001$). Two prospective, tandem studies showed conflicting results. Once again Hoffmann and colleagues showed significantly low adenoma miss rate with i-scan compared to WLI (30% and 62.5%, $p<0.001$)(85). A back-to-back study by Hong et al demonstrated no significant difference in ADR (36.5% and 31.9%, $p=0.54$) and adenoma miss rate (19.3% and 22.9%, $p=0.69$) comparing WLI and i-scan(86). The largest prospective, randomized trial comparing i-Scan with HD WLI involving 1936 patients showed promising results(87). Polyps and adenomas were consistently detected more frequently in the i-Scan cohort, 56% of the i-Scan group patients had a polyp of any type detected compared to 47% in the control group ($p = 0.03$). Adenomas were detected more frequently in the i-Scan group compared to the WLI group (33% and 27%, $p = 0.033$). Significantly more diminutive adenomas were found in the i-Scan group compared to the control group (40.2% and 28.0%), $p < 0.01$)(87).

1.5.6.4 *Blue Laser Imaging (BLI)*

Light amplification by stimulated emission of radiation (LASER) endoscope system (LASEREO; Fujifilm Co, Tokyo, Japan) was developed in 2012. This novel system allows for BLI, BLI- bright and linked colour imaging (LCI) to be performed as modes of narrow band observation. Recently, Fujifilm introduced another endoscope system using four light emitting

diodes (LED) positioned at the tip of the endoscope. This system enables BLI and LCI with an LED light source instead of a LASER light source(88).

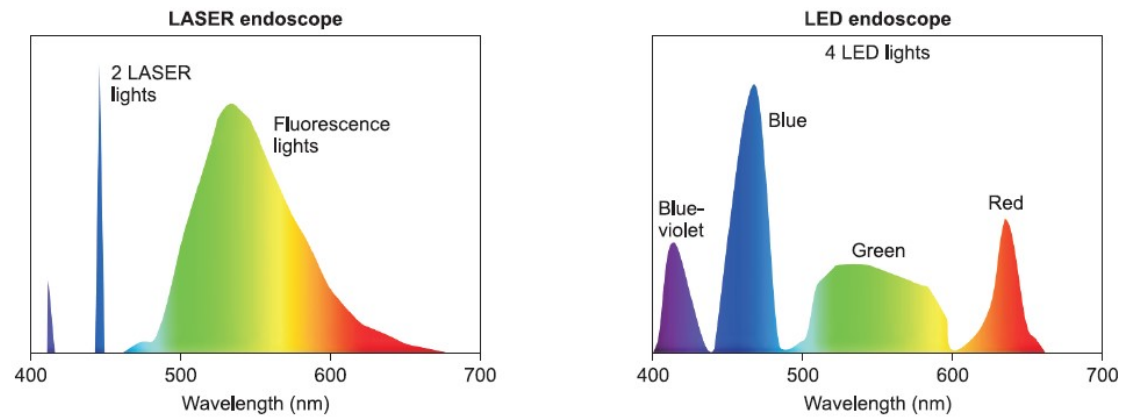


Figure 6. Characteristic of laser and LED system. Adapted from Yoshida et al.

Two types of lasers with wavelengths of 410 and 450 nm are used. The 450-nm laser irradiates phosphor to produce illumination similar to that obtained with a xenon lamp. The combination of strong 450-nm laser light and fluorescent light provides an illumination that is almost equivalent to that of WL (Figure. 5). The 410-nm laser emits narrow-band light. The BLI light is a combination of strong 410-nm laser light, weak 450-nm laser light, and fluorescent light. BLI with or without magnification is useful for acquiring mucosal surface information such as surface blood vessel and structure patterns (Fig. 6).^{11–13} By increasing the ratio of 450-nm laser light slightly rather than BLI mode, a BLI-bright mode can be set with a stronger fluorescent light (Fig. 6). The distant view of BLI-bright mode is brighter than that of BLI mode(89).

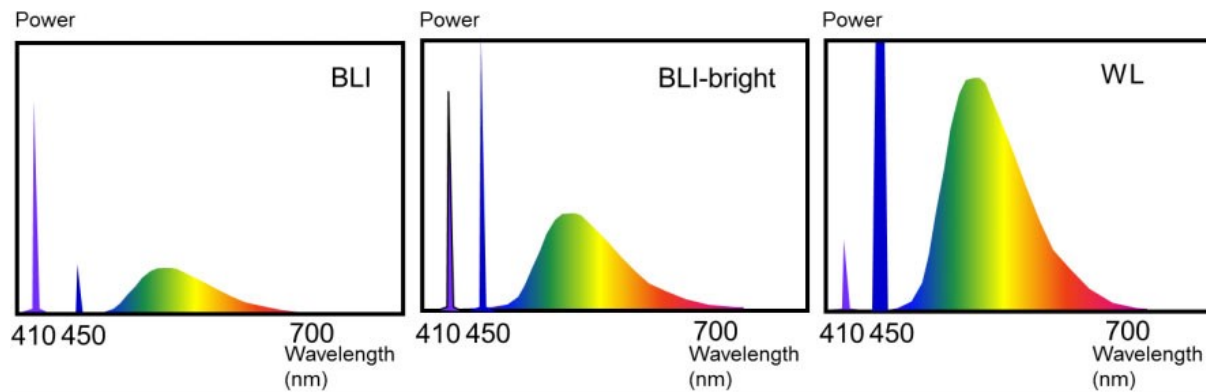


Figure 7. Combination of a 410nm laser, a 450 nm laser and fluorescent light provides illumination for BLI, BLI bright and WL. Adapted from Yoshida et al.

Only a handful of studies assessed the role of BLI and LCI on polyp detection. A randomised study, comparing BLI with WLI (total of 182 patients) showed a significant improvement in polyp detection rate (59.8% and 40%, $p=0.008$) and ADR (46.2% and 27.8%, $p=0.01$) with BLI(90). Another study by Fujimoto and colleagues assessed 200 still images containing SSA/Ps by 6 expert and non-expert endoscopists, using WLI, BLI, BLI-bright and LCI. LCI showed the highest SSA/P detection rate among the 4 mods for expert ($86.7\pm6\%$, $p<0.01$) and non- expert endoscopists ($72.7\pm11.5\%$, $p<0.01$) and significantly higher than WLI(91).

In summary, EC especially NBI and i-Scan improved the detection of diminutive polyps. Recently BLI and LCI have shown promising results to improve ADR and SSA/P detection rate. However, none of the modalities showed a sustainable improvement in ADR. Hence, the routine use of EC is not currently recommended to improve ADR in screening or surveillance colonoscopy.

1.5.7 Other factors influencing the polyp detection

Few studies suggest that the scheduling of colonoscopy procedure influences the performance. It was suggested that ADR was higher for morning procedures when compared to procedures performed in the afternoon(92, 93). This observation was not backed up by other studies(94,

95). Data from the English National bowel cancer screening programme suggests ADR may drop off as a list progresses, presumably due to operator fatigue(92).

1.5.8 Artificial intelligence and polyp detection

In order to overcome human error, artificial intelligence (AI) is gaining more attention. Karkanis and colleagues first reported a computer aided detection (CADe) system for colonic polyp detection and achieved a >90% detection rate(96). Another pilot study to evaluate the performance of CADe system, consisted of 155 polyp videos and established that the CADe polyp detection rate was 94%, although there was a high false positive rate of 60%(97).

1.6 Polyp characterisation and optical diagnosis

Current practice mandates that all small polyps detected during colonoscopy should be resected and sent for histopathological assessment to determine the histopathological polyp sub type (adenoma, hyperplastic, inflammatory or more recently sessile serrated lesion), as colonoscopic surveillance intervals are influenced by histological features of polyps (i.e. adenoma, presence of villous features and high grade dysplasia)(4, 98). The majority of polyps detected at colonoscopy are classified as diminutive (<5mm) polyps and rarely harbour cancer or high risk features such as high grade dysplasia or a significant villous component(99, 100).

As diminutive polyps are of such limited significance, being able to diagnose adenomas in vivo would allow them to be resected and discarded, saving the costs associated with histopathology. Furthermore diagnosing distal hyperplastic polyps in vivo would allow for these to be left in situ (diagnose and disregard) reducing the risks associated with polypectomy(101). By implementing a resect and discard policy it is estimated that between \$ 33 million to \$ 1 billion could be saved annually in the United States(102).Recent generation HD colonoscopes with virtual or electronic chromoendoscopy have enabled the endoscopists' to attempt to predict the histological type of polyps in-vivo.

1.6.1 Chromoendoscopy

Chromoendoscopy involves spraying of dark coloured dyes, such as methylene blue or indigo carmine on to the mucosa using a spray catheter(103, 104). These dyes highlight the different patterns on the polyp surface (pit pattern). These patterns were described by Kudo and colleagues using magnification colonoscopes and have been shown to differentiate HPs from adenomas(105). A prospective study of 122 patients evaluated 206 polyps (<1cm) using SC, indigo carmine dye spray with and without magnification. Chromoendoscopy with magnification was significantly superior in differentiating neoplastic from neoplastic pathology ($p<0.0001$) compared to SC(106). Several other studies using dye spray with magnification have shown diagnostic accuracies between 80-96% to accurately predict histological sub types of polyps(107, 108).

1.6.2 NBI

The majority of studies assessed on EC have assessed NBI, a blue light optical imaging modality which enhances the mucosal architecture, especially the vasculature. Vascular density and pattern differ between neoplastic (adenoma) and non-neoplastic (hyperplastic) polyps, therefore NBI could help to distinguish them (109). A group of international experts have developed and validated a system to characterize small colonic polyps: the NBI International Colorectal Endoscopic (NICE) Classification(110). This classification uses mucosal colour, vessel, and surface pattern to differentiate between hyperplastic polyps and adenomas. It is applicable for non-magnified NBI imaging. The authors made a diagnostic prediction with high confidence in 75% of the 236 polyps (82% in adenomas; and 64% in hyperplastic). They achieved 88% accuracy, 98% sensitivity, and 95% NPV for diminutive polyps. A meta-analysis by Wanders and colleagues evaluated real time optical diagnosis by NBI and showed an overall sensitivity 91% (95% CI 88.6–93.0), specificity 85.6% (81.3–89.0), and real-time negative predictive value 82.5% (75.4–87.9)(111). However, most of the studies in the meta-analysis were carried out by expert endoscopists in academic

centres(112). Ladabaum and colleagues prospectively evaluated real-time optical diagnosis of polyps with NBI by community-based gastroenterologists(113). This study showed inferior results when compared to the academic centres: sensitivity, specificity, and NPV of 85%, 78% and 91%, respectively. New NBI system with near focus might offer a solution for this discrepancy as the near focus image may provide a more detailed view of the surface architecture. Singh and colleagues assessed 149 polyps using the Olympus 190 series Exera III, NBI system with dual focus (DF) capabilities(114). The Overall accuracy of 97% was achieved with NBI-DF when compared to final histopathology and 97% accuracy for post-polypectomy surveillance interval based on the endoscopic prediction. Rather impressively the NPV for diminutive recto sigmoid polyps for adenomatous histology was 100% when NBI-DF was applied.

Table 2. NICE classification. Adapted from Hewett et al(110).

NICE Criterion	Type 1	Type 2
Colour	Same or lighter than background	Browner relative to background (colour arises from vessels)
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular, or branched white structures surrounded by brown vessels
Most likely pathology	Hyperplastic	Adenoma

It is often difficult to differentiate hyperplastic polyps (HP) from SSA/P on white light endoscopic examination. Yamada and colleagues performed a retrospective image evaluation study in which 242 NBI lesions were evaluated by 2 experienced endoscopists(115). Multivariate analysis demonstrated that the presence of Dilated and Branching Vessels (DBV) on the surface had a 2.3-fold odds ratio (95% CI 0.96-5.69) among SSA/P compared HPs. When DBV, proximal location and polyp size >10mm combined the positive predictive value reached 92% for SSA/P. Hazewinkel and colleagues investigated the NBI characteristics of 50

SSA/Ps images and suggested cloud like surface, indistinct borders, irregular shape and dark spots inside the crypts were NBI features associated with SSA/Ps(80).

1.6.3 FICE

Colour enhanced post processing image in real time enhances the mucosal vascular structures(82). Teixeira and colleagues proposed an endoscopic classification of the superficial capillary-vessel pattern of colorectal lesions to differentiate neoplastic polyps from non - neoplastic polyps: Type 1 and 2 are hyperplastic polyps, type 3 and 4 are adenomas and type 5 capillary pattern indicates invasive cancer(116). The authors analysed 309 colorectal lesions using the Teixeira capillary- vessel pattern classification and found 99.2% sensitivity and 94.9% specificity for neoplastic lesions.

A large prospective UK series by Longcroft- Wheaton and colleagues compared FICE with WLI and found that FICE improved the accuracy of in vivo diagnosis of adenoma from 75 % to 88% ($p < 0.001$)(117). FICE predicted post polypectomy surveillance interval with 97% accuracy. A meta- analysis by Wanders and colleagues examined 14 studies which used FICE to distinguish neoplastic polyps from non-neoplastic polyps in-vivo during screening colonoscopies(111) . FICE showed sensitivity of 91.8% and NPV of 83.7%.

1.6.4 I-Scan

i-scan provides enhanced images of the mucosal surface and the blood vessels through post-image processing. It enhances contrast and thereby mucosal surface detail including enhanced mucosal surface texture and sharpened views of surface vessels, thereby improving the visibility of blood vessels.

A recent meta –analysis of 11 studies using i-Scan to differentiate neoplastic polyps from non-neoplastic polyps, which included 925 patients with 2312 polyps demonstrated a sensitivity of 91.5% and specificity of 92.1%(118).

1.6.5 BLI

BLI, similar to NBI, enhances visualisation of vascular and surface structures. Yoshida and colleagues retrospectively examined 314 colorectal polyp images(119). The overall diagnostic accuracy of BLI without magnification for differentiating between neoplastic and non-neoplastic polyps (<10mm) was 95.2%, which was greater than that of WLI (83.2%).

Recent study described by Nakano and colleagues, analysed 748 polyps with BLI magnification and standard pit pattern analysis(120). The accuracy of distinguishing between neoplastic and non-neoplastic lesions was 98.4% using BLI magnification and 98.7% with pit pattern analysis. Several other studies showed the ability of BLI with and without magnification if differentiating HPs from adenomatous pathology and the accuracy varied between 85-95% (88, 119, 121). Furthermore, a study published by Wu et al analysed 94 polyps using LCI technology and showed a diagnostic accuracy of 91.5%(122).

EC is easy to use, cost neutral imaging technology that can allow the endoscopist to make clinically acceptable and accurate OD in-vivo. NBI has been extensively evaluated and has an established and validated classification system (NICE) which might be equally applicable to other forms of EC.

1.6.6 Modern photonic imaging

It is an exciting time for imaging in modern endoscopy. New emerging technologies are under various stages of pre-clinical and clinical trials. These technologies include confocal laser endomicroscopy (CLE), optical coherence tomography, Raman spectroscopy and multiphoton tomography (MPT) and many others (123). CLE gains a significant degree of magnification and resolution of mucosal images using a low power laser to induce fluorescence at a particular plane within the tissue. The emission of fluorescent light is then detected; confocal refers to alignment of the illumination and detection systems in the same focal plane(124). Several

studies have described the features of normal colonic mucosa and of adenomatous and HPs seen using CLE(125-129).

MPT depends on the absorption by tissue fluorophore of two or more protons, followed by emission of a single photon(130, 131). This technique exhibits the ability to allow real time study of human tissues cellular structural and functional details. Dual OCT and MPT imaging system, combine the structural information from OCT with the precise cellular imaging of MPT(132, 133).

1.7 Implementation of optical diagnosis

Initial clinical studies have suggested that optical diagnosis (OD) for diminutive colo rectal polyps could be feasible and safe in routine clinical practice.

Consequently, the American Society of Gastrointestinal Endoscopy (ASGE) developed a Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement for in vivo endoscopic assessment of diminutive polyps(134).

It states that the performance thresholds these technologies should be met prior to the adoption into clinical practice.

1. For a technology to be used to guide the decision on detect and disregard of rectosigmoid diminutive HPs. The technology should provide a 90% or greater NPV for adenomatous histology (with high confidence).
2. For colorectal diminutive polyps to be resected and discarded without pathologic assessment, when combined with the histopathological assessment of polyps larger than 5mm, should provide 90% or greater agreement in assignment of post polypectomy surveillance intervals.

However, recent reports suggest that OD performed by non-academic gastroenterologists could not reproduce similar results. Therefore, certain key steps should be followed before translating OD into general colonoscopic practice(135, 136). Furthermore, a recent update on ‘implementation of OD of colorectal polyps’ highlighted the following areas, discussed below(136).

1.7.1 Training and competency assessment

The knowledge and skills required to perform OD can be learned by people with varying experience in colonoscopy. Ignjatovic and colleagues from St Mark’s Hospital used a still image based teaching module to teach differentiation between adenomas and HPs(137). They showed improved accuracy and specificity of OD for all group of participants which included novices, trainees and experienced colonoscopists after a short training module ($k = 0.56, 0.7$ and 0.54 respectively). Recently IJspeert and colleagues developed and validated the first integrative classification method for endoscopic differentiation of small and diminutive adenomas, hyperplastic polyps and sessile serrated polyps(138). In a still image evaluation setting, introduction of the WASP (work group serrated polyps and polyposis) classification (figure 8) significantly improved the accuracy of OD overall and proved to be sustainable after 6 months. Overall accuracy of OD improved from 63% before training to 79% after training ($p < 0.001$) and remained at 76% after 6 months. This study highlighted the importance of continued training and re-assessment of individuals who perform OD to maintain the threshold. The fact ex vivo training does not necessarily translate into actual clinical practice was highlighted by the study by Ladabaum and colleagues(113). In an evaluation of real-time OD with NBI, only 25% of gastroenterologists assessed polyps with $\geq 90\%$ accuracy while more than 83% of gastroenterologists performed with $> 90\%$ accuracy ex vivo. These findings suggest that in vivo training with feedback and assessment is needed before non-academic gastroenterologists are certified to perform OD in routine clinical practice.

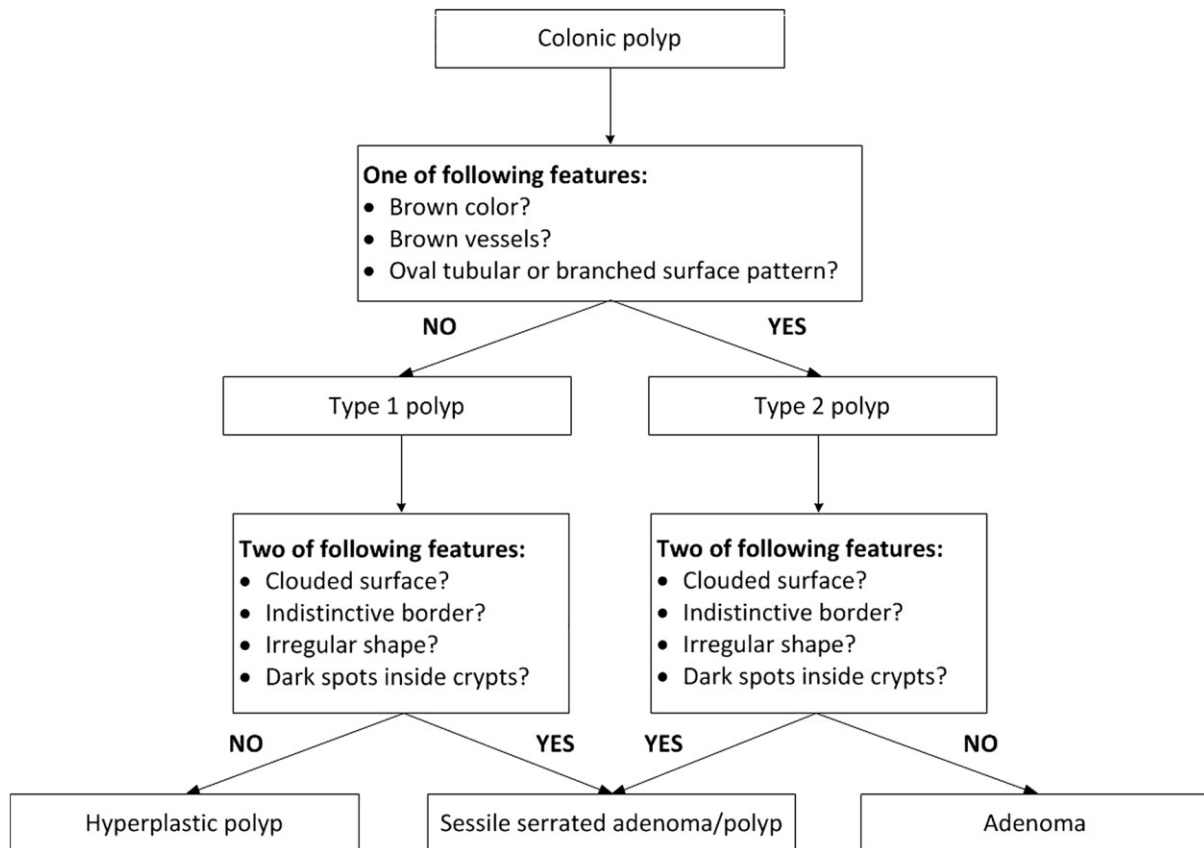


Figure 8. WASP classification Adapted from IJspeert et al.

1.7.2 Documentation

High quality image documentation of the polyp should be taken for quality assurance and medico – legal purposes(139). The question of whether high quality photos or video clips are necessary for documentation remains to be answered.

1.7.3 Other obstacles in implementing optical diagnosis in clinical practice

Understanding the precise prevalence of diminutive SSA/Ps in the rectosigmoid is of importance prior to implementation of optical diagnosis. As the ASGE PIVI report recommends detecting and disregard diminutive HPs in the rectosigmoid if novel imaging technologies achieve 90% NPV for adenomas(134). However, the PIVI document does not consider the prevalence of diminutive SSA/Ps, difficult to optically distinguish from HPs in the recto sigmoid(140). SSA/Ps should not be left in-situ due to the malignant potential of these

lesions. Only few studies have attempted to define the precise prevalence of SSA/Ps in recto sigmoid colon(141, 142). Furthermore, number and size of the SSA/Ps are now taken into account in determining the surveillance interval. For the above-mentioned reasons, the prevalence of SSA/Ps and discrimination of HPs and SSA/Ps may be important prior to the implementation of optical diagnosis.

Endoscopists need to be competent in OD prior to implementation in routine clinical practice. However, there is currently no competence framework or quality assurance methodology for maintaining competence.

1.8 Artificial intelligence and optical diagnosis

Deep learning-based AI model for real time assessment of endoscopic videos images of colorectal polyps show promising results. 106 diminutive polyps were assessed and the accuracy, sensitivity, specificity, NPV and PPV of the model to differentiate HPs from adenomas were 94%, 98%,83%,97% and 90% respectively(143). Similar deep learning approaches are under development and will be in use in the near future. Although these systems may come into daily practice the final decision and responsibility on OD will be made by endoscopists who will need to be fully competent and accredited in making accurate optical calls. This push for new technology makes a robust and rigorous training, accreditation and quality assurance programme even more important.

1.9 Hypothesis

Can changes to factors that influence the quality of colonoscopy improve polyp detection and characterisation to reduce missed polyps and help to achieve optical diagnosis of polyps in routine clinical practice.

1.9.1 Improving polyp detection

Complete colonoscopy and a systematic and meticulous examination of the entire colonic mucosa is necessary to enhance polyp detection. Wide angle colonoscopes have been shown to improve polyp and adenoma detection.

Aim: To evaluate the role of an extra wide-angle viewing colonoscope on polyp detection in colorectal models.

There is a difference in colonic configuration during the insertion and withdrawal phases of the examination. It is unclear whether additional careful examination during insertion is complementary to examination on withdrawal alone.

Aim: To assess whether inspection on insertion and withdrawal increases ADR in bowel scope screening procedure (a randomised controlled study).

Disposable distal attachments (Endocuff, Cap, Endorings) have demonstrated an increase in adenoma detection. The Endocuff and the plastic cap are the most established devices for improving adenoma detection.

Aim: To compare the performance of Endocuff vision and the cap in a tandem study.

1.9.2 Polyp characterisation and optical diagnosis

The ability to characterise diminutive and small colo-rectal polyps in vivo would lead to significant time and cost savings associated with the procedure. Electronic chromoendoscopy technologies have changed how we characterise colorectal polyps and the validated NICE classification is now widely established and familiar to a wide section of the colonoscopy community.

Aim: To validate whether the NICE classification can be utilised to characterise small colorectal polyps imaged using BLI technology.

The ASGE and ESGE recommend not resecting diminutive hyperplastic appearing polyps in the recto sigmoid colon. Hence, it is vital to define the true prevalence of hyperplastic and SSA/Ps in the distal colon prior to implementation of ‘detect and disregard’ policy.

Aim: To determine the prevalence of SSA/Ps in the distal colon at screening colonoscopy and flexible sigmoidoscopy procedures.

The learning curve of optical diagnosis for trainees has not been explored adequately as most of the trials to date have been performed by experienced operators.

Aim: To evaluate the minimum number of colorectal lesion assessments needed to achieve and maintain optical diagnostic competency for trainee gastroenterologists.

1.9.3 Thesis strategy

Chapter 1 reviews the aetiology of CRC, evolution of colonic polyps and the importance of improved polyp detection and characterisation at colonoscopy. The published evidence for the current advanced colonoscopy techniques and novel technologies are described.

Chapter 2 describes the proportion of missed colonic polyps in bowel cancer screening population.

Chapter 3,4 and 5 explores ways to improve polyp detection using advanced technology and novel devices. Chapter 3 deals with the potential of an extra wide-angle viewing colonoscope to improve polyp detection. Chapter 4 evaluates a procedural change in examination practice, i.e. careful examination of mucosa during insertion through the sigmoid to improve adenoma detection. Chapter 5 compares the efficiency of two distal attachments (Endocuff Vision and the cap) in polyp detection.

Chapter 6 describes the importance, development and application of a novel colonoscopy efficiency marker as a new metric of colonoscopy quality.

Chapter 7 investigates the new BLI technology and the validity of NICE criteria for BLI images.

Chapter 8 assesses the prevalence of serrated polyps in recto sigmoid area to inform practice regarding the detect and disregard optical diagnosis strategy.

Chapter 9 explores the learning curve of optical diagnosis in trainees using cumulative summation technique.

Chapter 10 draw together conclusions from studies conducted in the thesis and suggests further directions for research into polyp detection and characterisation.

Chapter 2

Missed colo-rectal polyps: an experience from the National Health Service Bowel Cancer Screening Programme

2.1 Background and aims

Several back-to-back colonoscopic studies reported that a significant number of colorectal polyps are missed during colonoscopic examinations, even when the procedures were performed by experienced endoscopists. The polyp miss rate described in the literature varied between 6-28%(27,144-145). Quality of a colonoscopy examination depends on various factors: optimal bowel preparation, ability to visualise the mucosa in front and behind the folds, colonoscopy technique, image quality and endoscopists experience in detecting significant pathology. Inattention to any of these factors would compromise the quality of the overall examination(146).

Even with a systematic, and meticulous examination technique, some areas of the colon are difficult to visualise(147). In a CT simulation study, East et al estimated that only 87% of the colonic surface area was routinely visualised during a standard colonoscopy(148). The ‘blind spots’ are located in the flexures, behind rectal valves and the ileocaecal valve and on the proximal sides of the folds(149). In addition, polyps smaller than 10mm, adenomas with flat morphology and SSA/Ps with indistinct borders and covered with mucous are more likely to be missed(150-152). Several techniques and technological advances have been developed to improve the quality of colonoscopy. Frequent position changes, routine use of antispasmodics and devices to improve the mucosal visibility (third eye retro view scope, wide angle high-

definition scopes, transparent cap, Endocuff)(42,49,56,60,66,153-156). Despite advancement in technologies and improved training in polyp detection, the polyp miss rate continues to be a significant challenge in routine clinical care and a major factor in the development of post colonoscopy colorectal cancers(157).

Participants testing positive for faecal occult blood or those with polyps at flexible sigmoidoscopy subsequently undergoing colonoscopy, within the National BCS programme, have a relatively high incidence of colonic polyps and hence are at risk of post colonoscopy colorectal cancers if polyps are missed. We designed this prospective study to estimate the polyps miss rate in BCS participants. All screenees were colonoscoped by experienced and accredited colonoscopists.

2.2 Methods

2.2.1 Study population

Patients who were scheduled for a post polypectomy surveillance colonoscopy, between July 2015 and July 2016 following an index colonoscopy (within last 3 years) were enrolled: patients who had multiple adenomas (more than three) or large (>10mm) adenomas at index colonoscopy were scheduled to undergo either one year or three yearly surveillance colonoscopies as per BSG post polypectomy surveillance guidelines. In all patients' index colonoscopy was performed as a screening (FOBT positive) or surveillance colonoscopy as part of UK national BCSP.

Patients who had a previous surgical resection of the colon, inflammatory bowel disease and polyposis syndromes were excluded from the study.

The study was conducted as a quality evaluation of missed colorectal polyps in BCSP. This study was reviewed and approved by North west London Hospitals NHS Trust review board (SUR.StM.17.001).

2.2.2 Colonoscopy procedure

Patients were prepared with either a combination of Senna and 2 sachets of magnesium citrate (CitramagTM, Sanochemia) or polyethylene glycol preparations (Klean prepTM, MoviprepTM). A standard consent form for undergoing surveillance colonoscopy was signed by all patients as part of good clinical and standard practice. Colonoscopies were performed with patients unsedated or under conscious sedation using midazolam and fentanyl. Patients were given 10-20mg of hyoscine N- butylbromide at the discretion of endoscopists. All procedures were performed by one of seven BCSP accredited colonoscopists, each having completed at least 5000 previous colonoscopies with caecal intubation rate of >96% and adenoma detection rate of >40%. The procedures were performed using Olympus 260 series colonoscopes (Lucera, Olympus, Tokyo, Japan). Disposable distal attachments (cap, Endocuff) were used only in a minority of patients (2%) and they were excluded from the analysis.

Patient demographics, procedural and performance variables of index colonoscopies were retrospectively retrieved from the screening database. Data were collected prospectively for the surveillance procedures at the end of each session by the research fellow. Histology of polyps were later retrieved from a clinical results database. Database was pseudo anonymised and stored in NHS password protected computers.

2.2.3 Primary and secondary outcomes

The primary end points of this study were presumed polyp, adenoma, and sessile serrated adenoma/polyps (SSA/P) miss rate for index colonoscopy. The secondary end points were miss rates of different size of polyps, advanced adenoma miss rate and any factors associated with missed adenomas.

2.2.4 Definition and calculation of missed polyps

Several studies highlighted that polyps <10mm grow at a slower pace and a proportion of polyps' regress in size over time. On average the volumetric growth of such polyps were 10-20% within a 3 year period(24-26). Hence, a polyp was presumed as “missed “at the index colonoscopy when they met the following criteria:

1. Polyp of any size detected at one-year surveillance colonoscopy
2. Polyps >5mm in size detected at 3-year surveillance

In addition, if a polyp was adjacent to a previous polypectomy scar was considered as a recurrence and not considered as a missed polyp. The miss rate of colorectal polyps was calculated as follows: total number of missed polyps/total number of polyps detected at index and surveillance colonoscopies.

2.2.5 Statistical analysis

All categorical data were expressed as proportions; all continuous data were expressed as mean and standard deviation unless otherwise specified. The baseline characteristics of missed polyps were expressed as percentages. A corresponding 95% confidence interval was also calculated using the exact binomial method. Similar calculations were performed for polyp subtypes. P values were calculated using Chi square or Fisher exact test where appropriate.

Subsequent analyses examined factors associated with missed polyps and adenomas. Due to the binary nature of the outcomes, the analysis was performed using logistic regression. The analysis was performed in two stages. Firstly, the separate association between each factor and missed polyps/adenomas was examined separately in a series of univariable analysis. Subsequently, the joint association was examined in a multivariable analysis, which has the advantage of adjusting the effects of each factor for the effects of the other variables. A

backwards selection procedure was used to retain only the significant variables in the final analysis.

2.3 Results

2.3.1 Patient demographics and procedure characteristics

A total of 241 patients (age range 55-79 years) underwent surveillance colonoscopy during this period. The index colonoscopy was performed for the following indications: screening procedure following a positive FOBT (50.2%), a significant finding detected during bowel scope examination (flexible sigmoidoscopy screening performed at the age of 55 - 41.5%) and surveillance following previous polypectomy (41.5%). Patient characteristics and procedure details are summarised in table 3. There were no significant differences in the quality of bowel preparation ($p=0.86$) and caecal intubation rate ($p=0.98$) between index and surveillance procedures ($p=0.86$). However, the withdrawal time (WT) was significantly longer for index colonoscopy when compared to surveillance procedures (one-year surveillance group $p=0.0001$, and three-year surveillance group $p=0.004$).

Table 3. Patient and polyp characteristic of index and surveillance colonoscopies

	Index colonoscopy	Surveillance colonoscopy
Number of patients		
One-year surveillance	90	90
Three-year surveillance	151	151
Sex (one/three year)		
Male	55/105	55/105
Female	35/46	35/46
Age (years)		
Median (one /three year)	63/66	-
Range (one/three year)	55-74/57-79	-

	Index colonoscopy	Surveillance colonoscopy
Indication (one/three years)		-
FOBT positive	57/64	90/151
Surveillance	18/82	-
Bowel scope	15/5	
Bowel cleansing score		
Excellent	45	56
Good	168	149
Adequate	28	16
Inadequate	0	0
Caecal intubation rate (%)		
One-year surveillance	99	99
Three-year surveillance	99	97.4
Withdrawal time (mins)		
Median (one year/three year)	19/12	11/10
Mean $\pm$ SD (one year/three year)	23.6 $\pm$ 14.2/13.9 $\pm$ 7.5	14 $\pm$ 9.4/11.6 $\pm$ 6.3
Number of polyps (one/three years)	457/315	211/258

2.3.2 Polyps miss rate

The overall presumed colorectal polyp miss rate and AMR for index colonoscopy were 21.8% (95% CI 19.6-24.2) and 21.6% (95% CI 17.6-20.3). Miss rates per polyp size and advanced histology sub types are shown in table 4. A significant proportion of SSA/Ps (51.6%) were missed during the index colonoscopy. However, no cancers were missed. Advanced adenoma miss rate was 13.8 % (95% CI, 9.2-19.4).

Table 4. Polyps miss rate by size and histological subtypes

	Total number of polyps	Number of missed polyps	Miss rate (%) (95% CI)
Polyps	1221	266	21.8 (19.6-24.2)
Adenomas	782	169	21.6(18.8-24.7)
<5mm	447	116	25.9(21.9-30.3)
6-9mm	202	43	21.2(16.2-27.5)
>10mm	133	10	7.5(4-13.4)
SSA/Ps	31	16	51.6(33.1-69.9)
Cancer	2	0	0

Adenomas with HGD	21	2	9.5(1.2-30.4)
Adenomas with villous histology	194	27	13.9(9.4-19.6)
Advanced adenomas	196	27	13.8(9.2-19.4)

2.3.3 Location of missed polyps

Location of missed adenomas and SSA/Ps are summarised in figure 9. Missed adenomas were scattered throughout the entire colorectum. Most of the missed adenomas were in the proximal colon (66%) when compared to the distal colon. Within the distal colon the majority of missed adenomas were situated in the sigmoid.

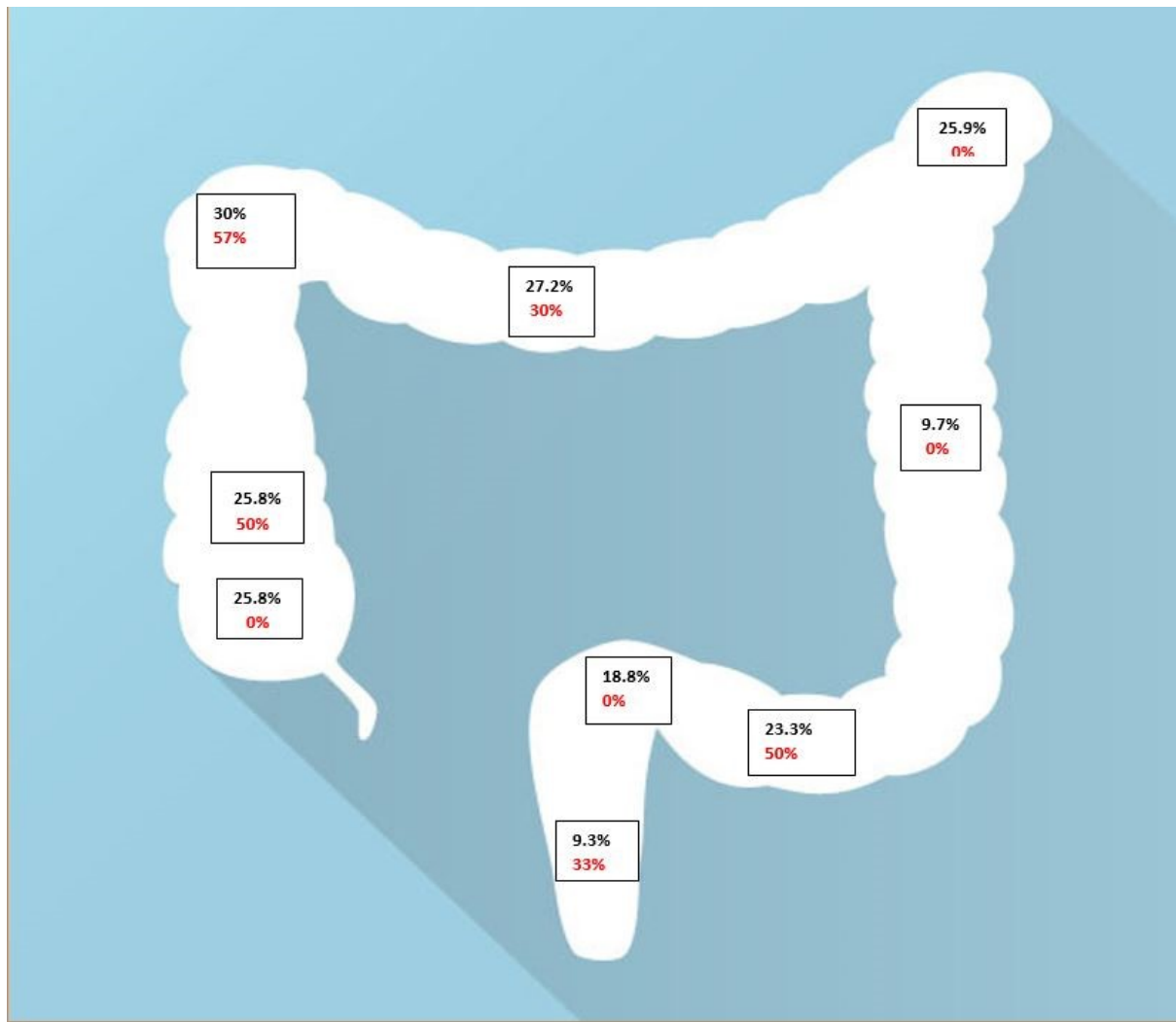


Figure 9. Location of missed adenomas and SSA/Ps. AMR and SSA/P miss rate are highlighted in black and red ink, respectively.

2.3.4 Factors associated with missed polyps

Table 5. Multiple logistics regression analysis of factors during index colonoscopy associated with missed polyps

Factor	Category	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Site	Distal	1	0.01	1	0.008
	Proximal	1.45 (1.08, 1.94)		1.49 (1.11, 1.99)	
Age (years)	≤ 60	1	<0.001	1	<0.001
	61 – 70	0.65 (0.46, 0.91)		0.63 (0.45, 0.88)	
	71+	1.26 (0.83, 1.92)		1.26 (0.83, 1.91)	
Sex	Male	1	0.80	-	-
	Female	1.04 (0.77, 1.41)			
Number polyps (*)	≤ 3	1	0.26	-	-
	4 – 5	1.28 (0.87, 1.89)			
	6+	1.32 (0.93, 1.88)			
Hyoscine butylbromide (*)	No	1	0.80	-	-
	Yes	0.84 (0.22, 3.20)			

* *Index colonoscopy*

Multivariate analysis was performed to examine the association between factors and missed polyps (table 5). A backwards selection procedure was used to retain only the statistically significant variables.

Patient, procedure, and polyp factors were analysed. Proximal location (p=0.008) and age more than 71 years (p<0.001) were independently associated with missed polyps.

2.3.5 Factors associated with missed adenomas

A similar set of analyses was performed to examine factors associated with a missed adenoma (table 6).

Table 6. Multiple logistics regression analysis of factors during index colonoscopy associated with missed adenomas

Factor	Category	Univariate		Multivariate	
		OR (95% CI)	p value	OR (95% CI)	p value
Site	Distal	1	0.01	1	0.02
	Proximal	1.61 (1.12, 2.31)		1.55 (1.07, 2.24)	
Age	≤ 60	1	<0.001		<0.001
	61 – 70	0.68 (0.45, 1.04)		0.68 (0.45, 1.04)	
	71+	1.64 (0.99, 2.72)		1.78 (1.05, 3.01)	
Sex	Male	1	0.75	-	
	Female	1.06 (0.73, 1.54)		-	
Number of polyps	≤ 3	1	0.06	1	0.06
	4 – 5	1.56 (0.97, 2.50)		1.78 (1.08, 2.93)	
	6+	1.67 (1.07, 2.60)		1.53 (0.97, 2.40)	
Hyoscine butylbromide	No	1	0.57	-	
	Yes	1.84 (0.22, 15.0)		-	

The results suggested that site and patient age (> 70 years) were significantly associated with a missed adenoma. A greater proportion of adenomas were missed in the proximal colon, with 24% missed in this location, compared to only 16% in the distal colon.

Adenomas were more likely to be missed in the oldest patient group, aged 71 and over. The odds of detection in this group were over 60% higher than in patients aged 60 or under and were even greater when compared to the 61-70 age group, which had the lowest adenoma miss rate. The presence of 4 or more polyps at index colonoscopy was associated with a greater adenoma miss rate, with odds of missing being around 60% higher than for colonoscopies where less than three polyps were detected.

2.4 Discussion

The most reliable method to evaluate polyp miss rate is to perform ‘tandem’ or ‘back-to-back’ colonoscopy. In studies employing this methodology, the second colonoscopy was performed

either on the same day or within 6 months of index colonoscopy. In such studies, the miss rate is usually expressed as the proportion of polyps (of any size) detected only during the second colonoscopy relative to the total number of polyps found during both procedures(28).

However, polyp growth and evolution studies highlighted that diminutive and small polyps progress slowly and at a low rate. A prospective observational study assessed 225 diminutive polyps for a mean follow up period of 7 years. During the follow up period 2% of polyps completely regressed, and the mean change in linear size was 3.6% per year(25). Tutein Noltheneus and colleagues reported a CT colonography surveillance study of 95 small polyps (6-9mm) up to 3 years. The results showed that after a 3-year surveillance interval, 38% of polyps remained stable in volume, while 14% completely regressed. Only 35% of polyps showed a 30% volumetric growth(24) . Both studies explicitly showed that most of the diminutive and small polyps progress slowly. In our cohort the second colonoscopy was performed 1-3 years after the index colonoscopy. During this period, some polyps could have had a change in the size and volume. We presumed that the change in polyp size was negligible within the first year and at 3 years the maximum growth difference would be smaller than 5mm. Hence, we considered the polyps which are larger than 5mm at 3 years and polyps of any size detected at one-year surveillance colonoscopies as missed polyps for the index procedure.

In the present study, the miss rate for colorectal polyps and adenoma were 21.8 % and 21.6 % respectively. These findings are consistent with those reported in the literature. A recent meta analysis evaluated six tandem colonoscopy studies assessed a total of 1650 polyps. The reported pooled polyp miss rate and AMR were 21% (95% CI:14-30%) and 22%(p=0.001) respectively(28).

Moreover, in our cohort most (94%) of the missed adenomas were smaller than 10mm in size. These findings corroborate with the results from previous tandem studies(27-28,144,158). However, the miss rate for adenomas larger than 10mm in size is slightly higher (7.5%) in our

study. The overall miss rate for large polyps in the meta analysis was 2%. But our miss rate was in line with the findings described by Rex et al, who reported a miss rate of 6% for large adenomas (27).

Just over 50% of SSA/Ps were missed during index colonoscopy. There are multiple reasons for the significantly higher miss rate in our population. Firstly, the total number of SSA/Ps were small (total of 31 polyps) and any small difference is exaggerated. Secondly serrated polyps predominantly located in the right colon where the bowel preparation is often sub optimal. Finally, they are often small and sessile and covered with mucous. Therefore, the endoscopist's undivided attention is necessary to detect and remove SSA/Ps(158-159). It is quite possible that the endoscopists concentrates on significantly larger adenomas during index colonoscopy and lacks concentration following detection of large adenomas could contribute to significant miss rates of SSA/Ps. A recent multi-centre study evaluated the endoscopist factors which influence serrated polyp detection. In this study a total of 104 618 colonoscopies performed by 201 endoscopists with variable degree of experience were analysed. Endoscopists characteristics associated with high detection for SSA/Ps were gastroenterology specialist training, more recent completion of training, higher annual colonoscopy procedure volume and higher rate of reported optimal quality of bowel preparation(160). Endoscopists attitude and behaviour towards a quality examination of entire colon could explain the higher missed rate of SSA/Ps. An attitude of 'I have already removed a significant large polyp in this patient and there is no need to look closer at this subtle benign hyperplastic looking polyp' may explain this phenomenon.

Sixty-five percentage of missed adenomas were in the proximal colon (proximal to splenic flexure). The most frequent site was ascending colon. This finding is in line with the results described by Lee and colleagues(158).

In the present study, in addition to the miss rate for polyps, we investigated the factors associated with missed polyps/adenomas. AMR was independently associated with age more than 71 years, proximal colonic location of polyps and more than 4 polyps detected during index colonoscopy. Findings described in this study are in line with those defined by Rex et al(27) and Bensen et al(145). We believe that hepatic flexure, caecum and ileocaecal valve area could be challenging to fully inspect compared to the left colon. The most likely explanation is, at these areas the colonoscope slips back leading to rapid slide by and inadequate visualisation(60).Recent studies suggested that disposable distal attachments such as EV prevents rapid slippage of the colonoscope and to improve visualisation of blind spots(66).

We highlighted the fact that, in patients with multiple polyps detected during the index examination, the risk of missing additional polyps/adenomas was significantly higher (OR 1.78 [95% CI 1.05-3.01]). This phenomenon was supported by several other studies. Bensen et al, evaluated 76 colonoscopy pairs performed within 120 days and concluded that, for each additional neoplastic polyp seen on the initial procedure, the risk of an additional missed polyp increased by 33%(145). One of the probable explanations is the ‘one and done’ phenomenon: reduced attention of the endoscopist after the detection and resection of the first adenoma. Furthermore, multiple polypectomies are time consuming and it may well be possible that the time constraints on endoscopists to complete the endoscopy list within the allocated schedule time plays a role. Most of these variables (human factors) are difficult to measure even in trial settings(159).

In our series, we did not find any correlation between miss rates and the quality of bowel preparation. The proportion of patients with fair or inadequate preparation was exceedingly small in our cohort to have any bearing on the results as 96% of patients had an adequate bowel cleansing. Several studies have demonstrated that longer withdrawal time (WT) is associated with higher ADR(161, 162). Our data did not support the association of prolonged WT and

improved polyp miss rate. There are two likely explanations for these results. Firstly, our participating endoscopists were experienced and BCSP accredited colonoscopists who perform high quality examinations and the WT was much longer than the recommended 6 minutes. In addition, evidence from BCSP in England showed that WT of longer than 10 minutes do not produce any significant increment in ADR(163). Secondly the measured WT in our study includes the time spent for polyp resection and retrieval. This is the reason for longer WT at the index colonoscopies, when compared to surveillance procedures as greater numbers of polyps were resected during the index procedures.

This study has several strengths and some limitations. The strengths include the fact that all procedures were performed by seven, highly experienced colonoscopists known to be persistently performing high quality examinations (ADR>40%, CIR >96% - unpublished data). Secondly, the enrolled population was homogenous as only the polypectomy surveillance cohort was included in the study.

Limitations include a single centre trial with little variation in the study population characteristics so the results may not be applicable to wider colonoscopy practice. Secondly, we did not collect the data on other factors associated with the development of polyps such as smoking, alcohol history, family history of polyps or CRC and body mass index. Thirdly, the second procedures were not performed immediately as we included 3-year surveillance procedures. During this period some de novo polyps could have appeared and grown rapidly. To minimise the impact of those polyps on the results, we considered polyps bigger than 5mm in our miss rate calculation.

In summary, significant miss rates for polyps still occur at colonoscopy within the UK National BCSP, even when performed by experienced endoscopists with high adenoma detection rates. Our study highlights the fact that increasing age, history of multiple polyps and proximal locations are risk factors for missed polyps. Endoscopists should pay more attention to these

higher risk groups when performing colonoscopies and perhaps schedule more time per procedure. Devices to aid in polyp detection might have particular utility in these higher risk groups.

Chapter 3

Does Extra Wide-Angle View Colonoscope (EWAVE) improve polyp detection rate when compared to Standard Colonoscope (SC): A randomised tandem non-clinical study

3.1 Background and Aims

Colonoscopy with polypectomy reduces risk of death from colorectal cancer and depends on the effective detection and removal of precancerous lesions. Despite improvements in colonoscopy imaging technology and colonoscopists training it remains as an imperfect tool(164). It has been reported that a significant proportion of adenomas and sessile serrated adenomas/polyps are missed (6-27%) during routine colonoscopy(27,28) leading to concerns regarding post-colonoscopy or interval cancers(156, 165). Several factors contribute to poor detection including inadequate or sub optimal bowel preparation, incomplete procedures, shorter withdrawal times and poor visualisation of the total colonic mucosa(5,10). Arguably the single most important factor is inability to visualise polyps at blind spots in the colon; behind the haustral folds, major flexures and around the ileocaecal and rectal valves. Endoscopists continue to explore various methods and technologies to improve adenoma detection such as frequent position changes, routine use of antispasmodics and devices placed on the tip of the scope (Endocuff, Endorings and caps) to improve the mucosal visibility(43,60,67-68,154,166-168).

There is also interest in new colonoscopes that effectively increase the field of view(169). This can be done by adding more optical windows or by widening the field of view. This preclinical study assesses the impact of a new wide field viewing scope on lesion detection.

The aim of this randomised non-clinical study was to compare EWAVE with SC for polyp detection rate on anatomic colo rectal models.

3.2 Methods

3.2.1 Extra Wide-Angle View colonoscope (EWAVE)

EWAVE is a prototype colonoscope with two lenses: one standard 140° angle forward view and a 232° angle lateral and backward view lenses. Views from both lenses are simultaneously displayed on a standard video monitor (Figure 10). This prototype scope has a variable stiffness shaft function and a 3.2mm wide channel for accessories.

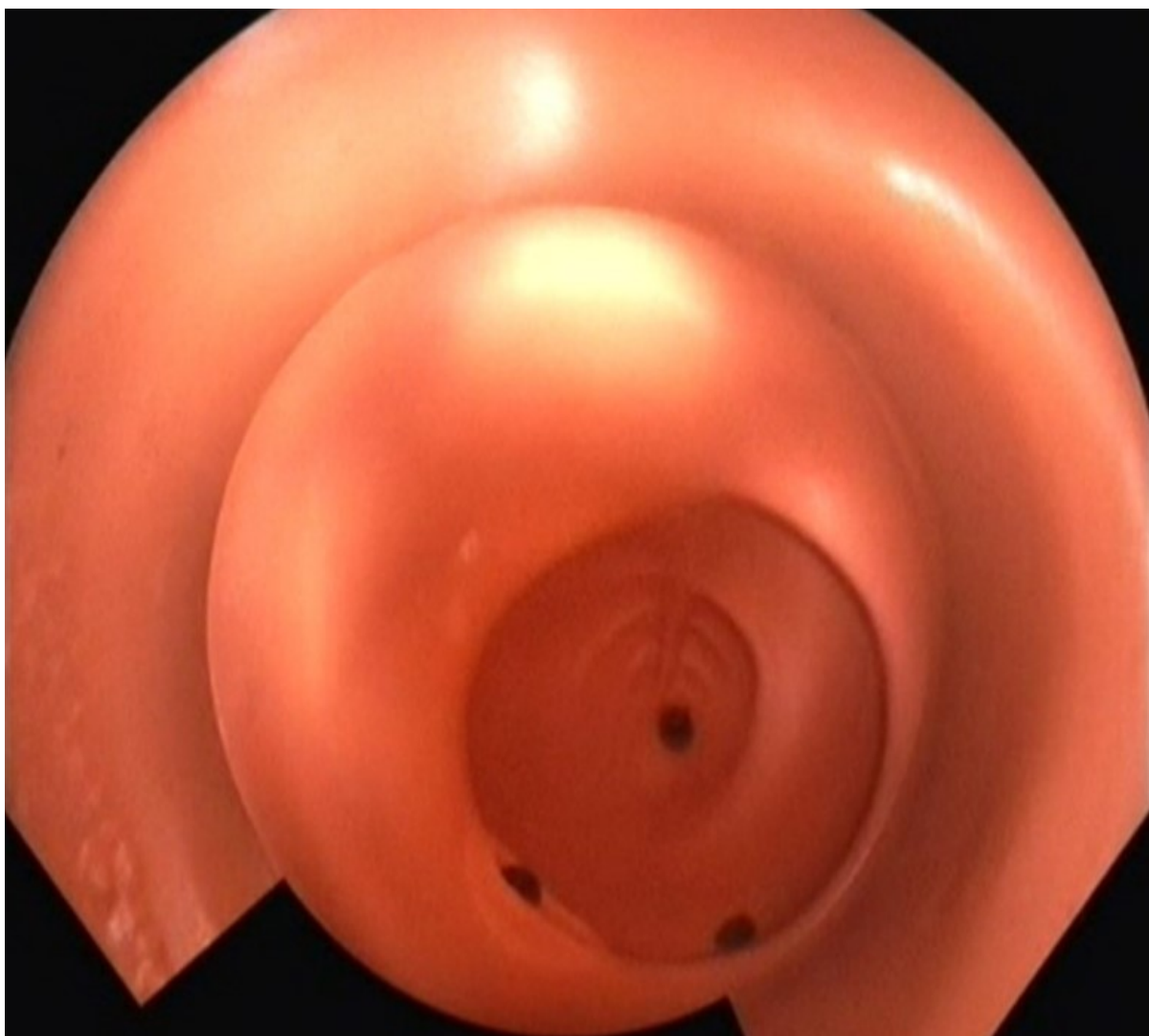


Figure 10. E-WAVE image. Images from forward and lateral view lenses are constructed and displayed as a single image. A sessile simulated polyp was visible on the lateral view lens.

3.2.2 Anatomic colorectal models

For the evaluation two in vitro silicone colorectal models (Kokone, Tokyo, Japan) were used. These are well demarcated anatomically correct representations of the colon and rectum. Two models were prepared with 18 (Model I) and 20 (Model II) simulated polyps of different sizes (2-15mm) at different locations throughout the colorectum. Polyps distribution was planned to keep equal numbers of polyps at the front and back of the colonic folds. Half of the polyps

were placed behind haustral folds while others were placed at easily detectable locations in the forward view. Polyps distribution and sizes of the simulated polyps were different for both models.

3.2.3 Study design and colonoscopic examination

This was a prospective, randomised non-clinical study. Endoscopists of different experience levels performed back-to-back colonoscopic procedures using a prototype EWAVE colonoscope and a standard colonoscope (CF260QL, Olympus, Tokyo, Japan) on the two models.

There were 11 Gastroenterology trainees and 4 nurse endoscopists with varying levels of colonoscopic experience participated in this study. Endoscopists performed back-to-back colonoscopic examinations of both models. The order in which they performed the examination first with SC or EWAVE colonoscope were randomised (Model I). On the second model, each endoscopist performed the procedure in reverse order to avoid any type II errors (Figure 11). All endoscopists were blinded to number of polyps, polyp site and size. None had any experience in using the EWAVE colonoscope prior to the study. All participants had two examinations on a different model with the EWAVE scope prior to the main study.

For each model during the examination, the following parameters were recorded: caecal intubation time, withdrawal time, site, and size of each detected polyp.

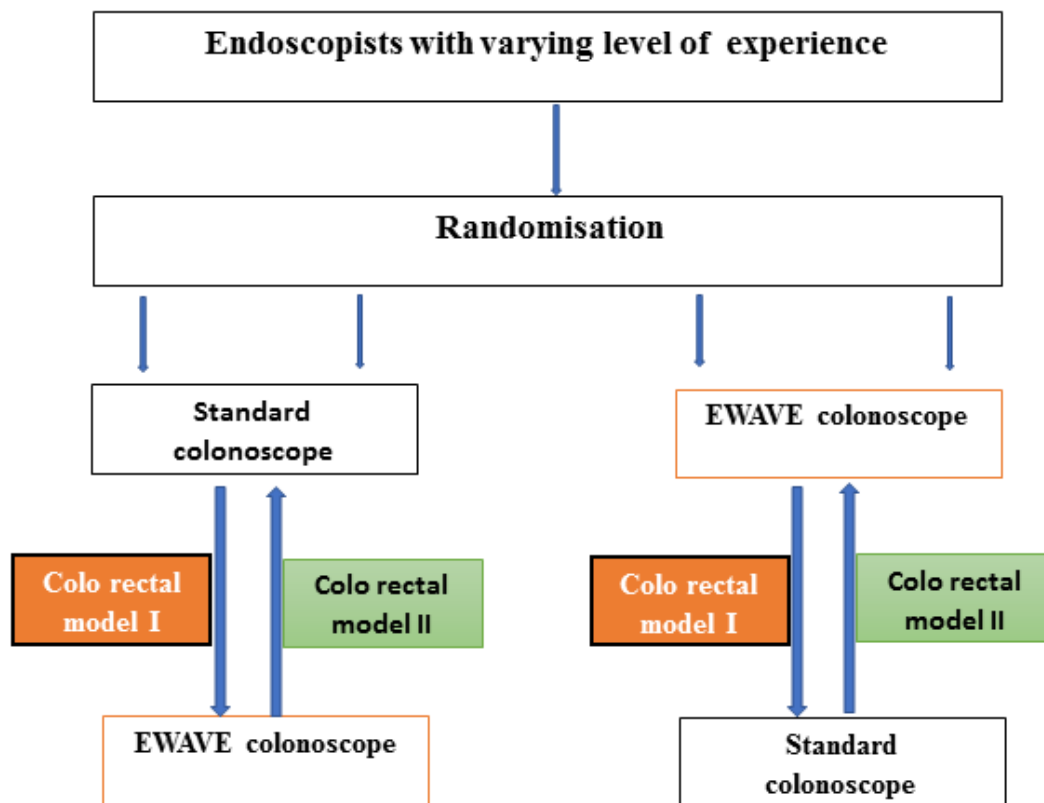


Figure 11. Study design

3.2.4 Primary and secondary outcome measures

The primary outcome of the study was to compare the simulated polyp detection rate (PDR) between EWAVE, and SC. Secondary end points were PDR per endoscopist, comparison of PDR per size, site and caecal intubation and withdrawal time.

3.2.5 Statistical analysis

Descriptive statistics were calculated for all measured variables and derived parameters. For continuous variables, Caecal intubation, withdrawal times, we calculated means, medians and standard deviations (SD). A Fisher exact test and t test were applied for testing the difference in number and percentage of polyps detected between both modalities. All tests used were 2

tailed, with $p < 0.05$ was considered statistically significant. All data analyses were performed using GraphPad Prism version 7.

3.3 Results

3.3.1 Polyp detection rate

All participating endoscopists' achieved 100% caecal intubation rate on both models. There was no significant difference in mean caecal intubation or withdrawal times (Table 7). The simulated polyp detection rate was significantly higher with the EWAVE colonoscope when compared to the standard colonoscope (79% and 90% respectively. $P < 0.0001$).

The mean PDR per endoscopist showed a similar trend on both models ($p = 0.03$ and $p < 0.0001$ respectively for model I and II).

Table 7. Procedure quality makers on both colorectal models

	Model I		p	Model II		p
	SC	EWAVE		SC	EWAVE	
Caecal intubation rate (%)	100	100	NS	100	100	NS
Caecal intubation time (mean $\pm$ SD)	3.7 $\pm$ 1.8	3.7 $\pm$ 1.4	0.89	3.1 $\pm$ 1.7	2.9 $\pm$ 1.7	0.8
Withdrawal time (mean $\pm$ SD)	4.9 $\pm$ 1.8	4.9 $\pm$ 2.1	0.91	4.8 $\pm$ 3.0	3.8 $\pm$ 1.6	0.3
Polyp detection rate (PDR % mean $\pm$ SD)	14.5 $\pm$ 1.8	15.9 $\pm$ 1.3	0.03	18.1 $\pm$ 1.5	18.1 $\pm$ 1.5	0.0001

3.3.2 Number of polyps detected as per size and segment

For each segment of the colon, the EWAVE colonoscope detected more polyps when compared to the SC (Table 8). There was a significant difference in simulated polyp detection at the recto sigmoid junction (12 and 6, $p = 0.04$), in the sigmoid colon (74 and 60, $p = 0.01$) and transverse colon (80 and 66, $p = 0.002$).

The polyp detection rate was higher with the EWAVE colonoscope for polyps of any size (table 9) and this difference was most pronounced for polyps between 6-9mm in size (89% and 73%, $p<0.0001$).

When the EWAVE colonoscopy was performed following a standard colonoscopic examination, more polyps were detected with EWAVE (Table 10). This finding highlight that the hidden polyps were detected significantly better with the EWAVE colonoscope ($p=0.04$ and $p<0.0001$ for model I and II respectively).

Table 8. Number and location of polyps detected by each modality

Location	SC	EWAVE	P value
Rectum	61	72	0.06
Rectosigmoid junction	06	12	0.04
Sigmoid colon	60	74	0.01
Descending colon	40	42	1.0
Splenic flexure	27	27	1.0
Transverse colon	66	80	0.002
Hepatic flexure	47	54	0.05
Ascending colon	56	54	0.5
Caecum and ICV	81	84	0.2

Table 9. Number of polyps detected by both modalities and the polyp detection rate as per polyp size

Size (mm)	SC No (%)	EWAVE No (%)	P value
All polyps	443/558 (79.4)	505/558 (90.5)	<0.0001
Less than 5mm	42/45 (93.3)	40/45 (88.9)	0.71
6-9mm	246/335 (73.4)	298/335 (88.9)	<0.0001
Greater than 10mm	155/178 (87.1)	167/178 (93.8)	0.05

Table 10. Variation in mean PDR in tandem colonoscopy on both colorectal models

	Model I p value	Model II p value
Standard colonoscopy followed by EWAVE	0.045	<0.0001
EWAVE followed by standard colonoscopy	0.28	0.08

3.4 Discussion

Our non-clinical study of simulated polyps suggests that, the use of a prototype EWAVE colonoscope improves polyp detection when compared to a standard forward-viewing colonoscope.

Several studies showed that, even experienced endoscopists can miss significant numbers of adenomas(27,144). Rex et al performed back to back colonoscopy examinations in 183 patients and reported an overall adenoma miss rate of 24% and 6% of missed adenomas were more than 1cm in size(27). Corley et al, highlighted that ADR is inversely associated with risk of interval colorectal cancer and death(11). ADR has become the single most important measure of colonoscopy quality and improving ADR is now a major goal of all colonoscopists(170,171).

Several different technologies and techniques have been proposed to improve ADR. Accessory devices such as the transparent cap, Endocuff and Endorings to stretch or splay out the haustral folds to improve visualisation behind colonic haustral folds have shown significant promise but with mixed results in clinical trials(60,66-68,154). However, recent systematic review and meta analysis comparing EAC and SC with a total of 6038 patients showed a significant improvement in ADR with Endocuff (RR=1.18, 95% CI, 1.05-1.32). Nine randomised controlled trial were included and showed a significant improvement in ADR for less experienced endoscopists (RR1.37, 95% CI, 1.08-1.74)(66).

A recent pooled analysis of back to back, tandem colonoscopy studies assessed the “technologies help to visualise back of the folds”, including the third eye retro view scope, full spectrum endoscope (FUSE) and Endorings, showed that the adenoma miss rates were significantly lower when these technologies were applied during colonoscopy ($p<0.02$)(172).

Conventional colonoscopes have a 140-degree visual window, recently increased to 170° but prototype instruments utilising an expanded single lens view of 210° have undergone preliminary analysis. In this clinical study total of 50 patients were randomised to undergo a colonoscopic examination either with a standard colonoscope or wide angle colonoscope. There was no difference between two colonoscopes in the detection rate for adenomas, but the polyp miss rate was lower with wide angle colonoscope (20.4% and 31.4% respectively, $p=0.046$). Colonoscopy withdrawal time was significantly shorter with wide angle colonoscope. These findings highlighted the fact wide angle colonoscopic examination improved efficiency of colonoscopy withdrawal as proximal side of the folds are readily visualised(169).

The EWAVE scope is a fundamentally new concept of widening the visual field to 242°. Images from forward and lateral view lenses are combined and displayed as one single image.

Another pilot study by Uraoka et al. using a colorectal model assessed the performance of the EWAVE colonoscope on polyp detection (173). This study showed superior polyp detection when compared to a standard forward viewing colonoscopy (68% and 51%, $p<0.0001$). Our study showed similar findings (90% and 79%, $p<0.0001$). The same authors published a clinical feasibility study using the EWAVE colonoscope. A total of 47 patients underwent a colonoscopy with EWAVE and found 5/6 (83%) of adenomatous polyps first detected with lateral/backward view lens. They concluded that the EWAVE colonoscope is safe and usable in clinical practice (174). The ability to perform polypectomies using the EWAVE scope has not been explored, although the instrument has a standard biopsy channel and polypectomy

would likely be performed after manipulating the polyp so that it is clearly seen in the standard forward view. The exit channel for accessories lies about 2-3mm proximal to the forward view lens (i.e lens and accessory channel are not at the same horizontal plane). This might prove to be a significant issue when performing polypectomies due to the difference in depth perception while placing the snare around the polyp. The forward view lens protrusion beyond the accessory channel might limit closer access to the polyp as well.

A strength of this study is the prospective randomised design using endoscopists with different levels of experience. Moreover, we compared the EWAVE scope to a standard forward viewing colonoscope and used different sizes of simulated polyps in different locations of the colon. Every endoscopist performed the procedure on both colorectal models in different order to minimise any bias.

Limitations of this study are that it was performed on a colorectal model using simulated polyps and in a single centre. The folds in the colorectal model used were not completely representative of real colonic haustral folds as they are made of hardened plastic and therefore do not distend to gas insufflation and cannot be easily manipulated with the tip of the colonoscope.

In summary, our pre-clinical study demonstrates that the use of an extra wide angle colonoscope significantly improves simulated polyp detection. The therapeutic ability of the novel colonoscope has not been explored in this study. Future clinical trials to assess polyp detection and resection using EWAVE in routine colonoscopy practice appear warranted.

Chapter 4

Does careful inspection of colonic mucosa during insertion and withdrawal improve adenoma detection: A randomised controlled trial (INWARD)

4.1 Background and Aims

Polyp detection strategies at colonoscopy tend to be focused on the withdrawal stage of the examination. Colonic examination is traditionally performed after passage of the colonoscope to the caecum with careful examination of the mucosa during the scope withdrawal phase. Once detected, polyps are removed during the withdrawal phase (175). However, in some locations within the colon such as the transverse colon and sigmoid colon polyps may be easier to detect during insertion rather than withdrawal (176). This could be due to stretching of the colon during insertion, making the bowel more tubular and reducing blind spots from haustral folds. During withdrawal, the colon is shortened, and the adjacent folds are brought closer to each other. On withdrawal colon is much straighter with greater fold definition and there is a tendency for the scope to fall backwards, particularly in the muscular sigmoid colon. Therefore, different areas of colonic mucosal surface may be exposed on insertion and withdrawal (175) and examination during the insertion phase may complement a careful standard examination during withdrawal.

Flexible sigmoidoscopy has been implemented since 2013 as part of the English Bowel cancer screening programme. The “bowel scope” examination is offered to the population at 55 years. Healthy adults can opt in for the examination between the ages of 56-59 years.

Recent reports suggests that ADR within bowel scope varies considerably (177). We propose a small technical alteration to improve ADR in bowel scope. A recent prospective trial highlighted that if polypectomy at colonoscopy was performed only during withdrawal, then 7 % of polyps were missed, when compared to performing careful inspection and polypectomy during both the insertion and withdrawal (178). To date, there are no studies instituted this methodology in flexible sigmoidoscopy screening procedures.

We hypothesised that careful inspection and polypectomy during both insertion and withdrawal would increase ADR due to a more complete visualisation of the distal colonic mucosa during “bowel scope” examinations.

The primary aim of INWARD (inspection on INsertion and WithdrAWal in bowel scope to improve Rate of adenoma Detection) study was to assess the impact of this intervention on ADR when compared to the conventional way of examining the colon during withdrawal alone.

4.2 Methods

4.2.1 Participants

Consecutive patients who were referred for a bowel scope examination between March 2017 and July 2018, were invited to participate in this prospective randomised controlled trial at St Mark’s Hospital, London, United Kingdom.

Research protocol was reviewed and approved by NHS BCSP research committee and approved on the 26th of February 2016 (ID 167). The study was reviewed and approved by the South east coast – Brighton & Sussex research Ethics committee on the 24th of January 2017 (16/LO/2131), and all subjects gave informed consent. The trial was registered at Clinicaltrials.gov (NCT03254030). We followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines in reporting the study(179).

4.2.2 Randomisation

This was a prospective, randomised, parallel group study. Participants were randomised in a 1:1 ratio to have bowel scope during which the endoscopist inspected the mucosa during insertion and withdrawal (study group) or inspected only during withdrawal (control group). Randomisation results were obtained using a computer-generated sequence with a block design (8 participants per block), kept in sealed opaque envelopes. Just before starting the examinations, the research assistant opened the envelopes to reveal the allocation.

4.2.3 Bowel scope examination protocol

All participants had a phosphate enema two hours prior to the procedure. Patients with poor bowel preparation (semi solid stools that could not be suctioned or flushed away with water) were given a 2nd phosphate enema through the scope channel and the procedure was repeated. Patients with poor bowel preparation despite two enemas were excluded. Written informed consent was obtained from all patients. Procedures were performed either with Entonox analgesia or without any medications. None of the patients were given conscious sedation or propofol. All procedures were performed by one of five bowel cancer screening accredited gastrointestinal fellows in training (Bowel scope accredited).

A research assistant recorded insertion and withdrawal times using a stopwatch with the aim of equal total examination times between the arms. We followed methodology described by Hewett et al, on a similar study performed in screening colonoscopy (175). Additional inspection time of 3 minutes on insertion or withdrawal was allocated in addition to a standard 3-minute inspection on withdrawal recommended by NHS BCSP guidelines (180). For patients in the interventional arm, a systematic inspection was carried during insertion and withdrawal.

4.2.4 Study design

In the control arm the colonoscope was inserted efficiently with minimal washing or insufflation to beyond sigmoid colon. Careful and systematic examination of the colonic mucosa was performed entirely on withdrawal. A minimum of 6 minutes examination time was followed.

In the intervention arm inspection was carried during insertion and withdrawal. A minimum inspection time of 3 minutes on insertion and 3 minutes on withdrawal was followed to keep total inspection times equal in both arms of the study (Figure 12).

When a polyp was detected, the endoscopist made a note as to whether the pathology was detected on insertion or withdrawal. Polypectomy was performed either in the insertion or withdrawal phase at the discretion of endoscopist.

4.3 Primary and secondary outcomes

The primary end point of this study was to compare ADR between the control and study group.

The secondary outcome measures were:

1. Mean number of adenomas detected per patient (MAP) between control and study arms.
2. Polyp Detection Rate (PDR)
3. Total procedure times
4. Detection rate of clinically significant polyps (i.e. serrated lesion or adenoma >1cm, adenomas with villous features on histology or the presence of high-grade dysplasia.
5. Patients' discomfort during the procedure

6. Effects of queue position (timing on list) of the procedure on ADR

4.4 Statistical methods

4.4.1 Sample size calculation

The study was powered to detect a difference in ADR between groups. Lowest ADR for bowel scope examinations in our institution was 6%. A difference in ADR of 10% would be of clinical importance. Therefore, to demonstrate a 10% absolute increase in ADR with a 5% significance level and 80% power using a two-sided test it was calculated that 239 patients per group were required for the study. Total number of patients needed to be recruited would be 478. To accommodate the number of incomplete procedures due to poor tolerance and sub optimal bowel preparation an additional 5% were enrolled.

4.4.2 Analysis

The primary outcome was ADR, a binary measure with adenomas either detected or not detected. This outcome was compared between groups using the Chi-square test.

Categorical secondary outcomes were analysed using the Chi-square test, as the primary outcome, or using Fisher's exact test for rarer outcomes. Continuous Variables that were found to have a skewed distribution (number of adenomas, procedure times) were compared between groups using the Mann-Whitney test. The unpaired t-test was used for continuous variables found to be approximately normally distributed (patient comfort score). Secondary outcomes p value was exploratory rather than generated by the hypothesis (significance of secondary outcome measures were not considered during sample size calculation).

A final analysis examined the impact of queue position on ADR. Patients were divided into two groups based on their queue position, either an early position (positions 1-4) or a late position (positions 5-8). A small number of patients had a queue position of either 9, 10 or 11,

and were excluded from the comparison. The Chi-square test was used to compare ADR between the two groups.

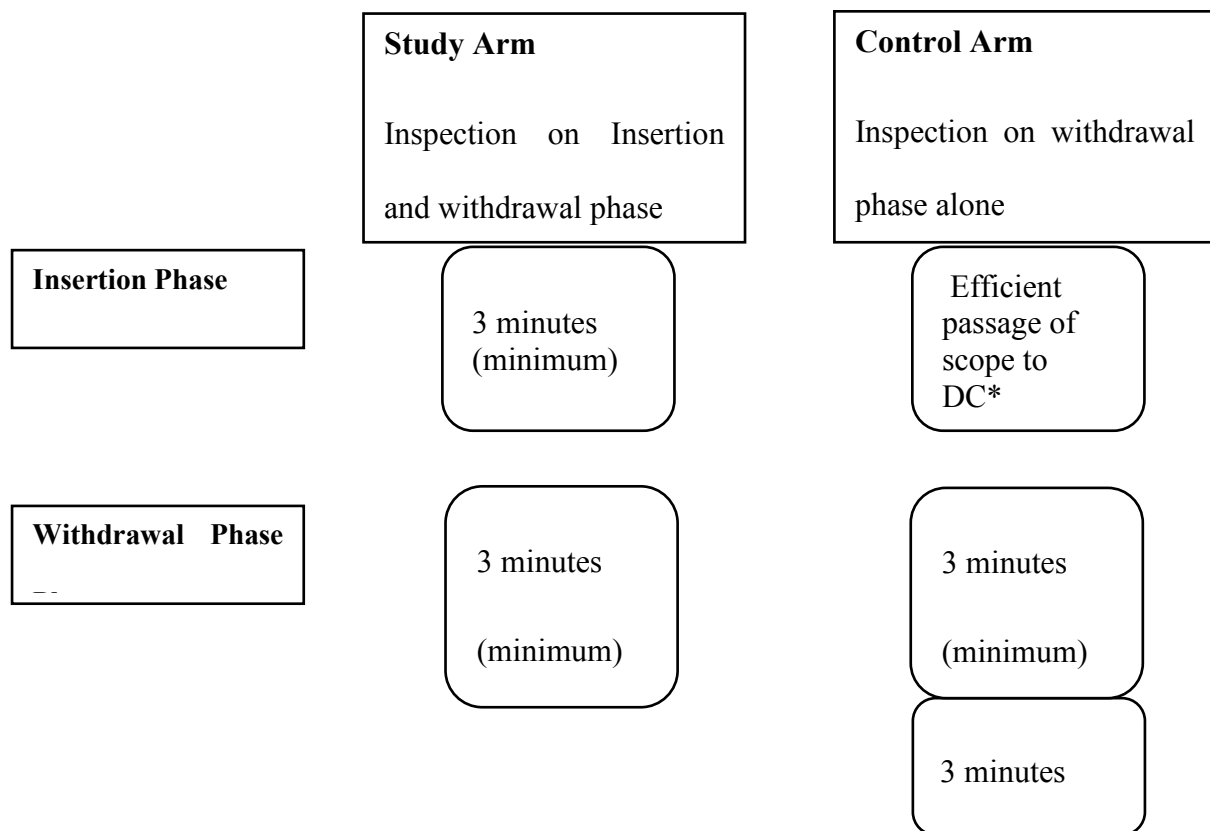


Figure 12. Study design

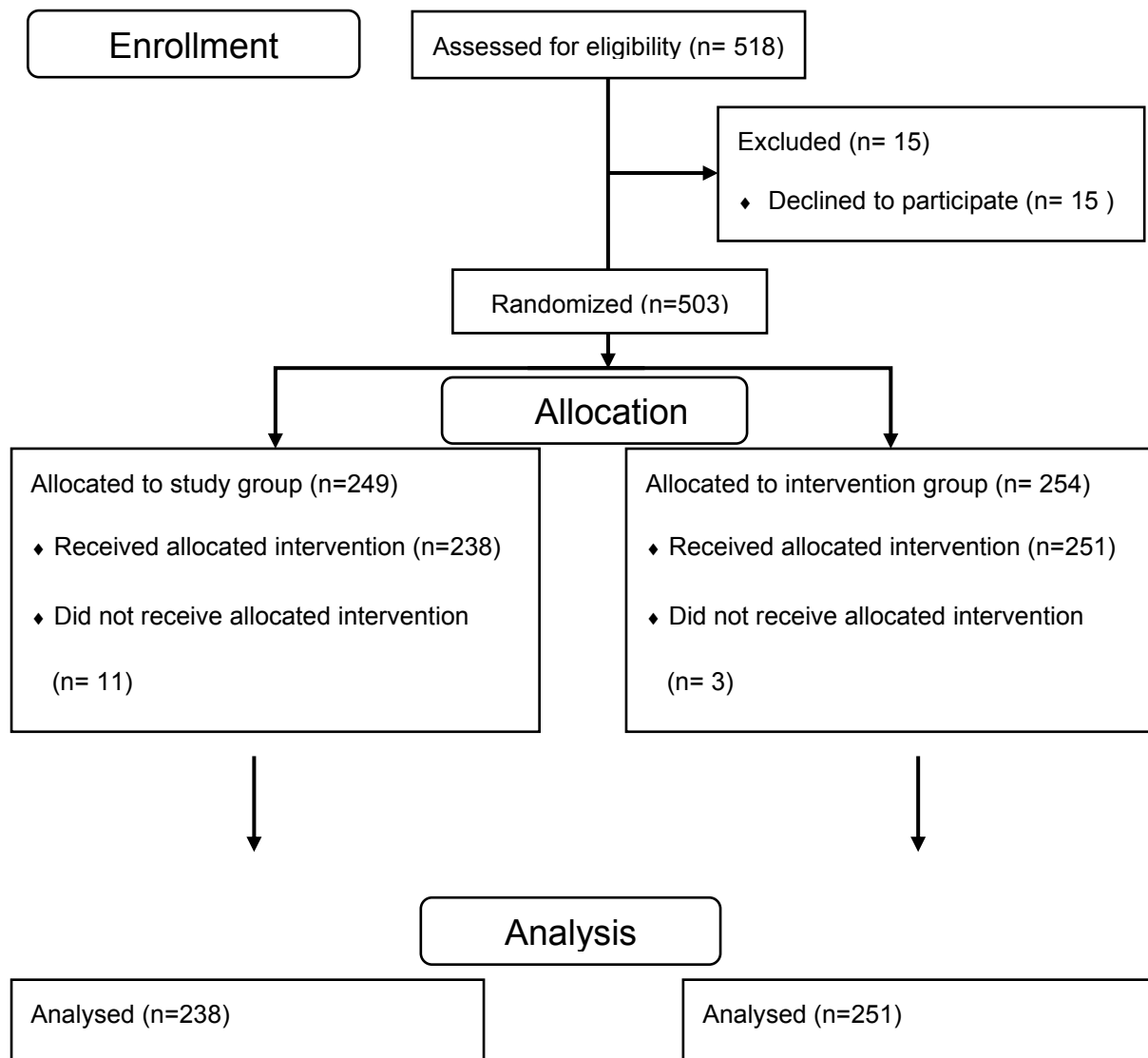


Figure 13. CONSORT Flow Diagram of INWARD trial

4.5 Results

4.5.1 Participants

A total of 518 patients were invited to participate in the study. 15 patients declined to participate. Five hundred and three patients consented to participate and were randomised. A total of 14 participants were excluded from the trial following randomisation for reasons mentioned in Figure 13(CONSORT flow diagram). There was no statistically significant difference in age, sex, or co-morbidities between the study arms. All the procedures in which endoscopists reached beyond sigmoid colon, were considered complete and included in the

analysis. Baseline demographic and clinical characteristics for patients who completed the trial are demonstrated in Table 11.

Table 11. Baseline characteristics of participants

	Control (n=238) Number (%)	Intervention (n=251) Number (%)	P value
Sex			0.89
Female	116(48.7%)	109(43.6%)	
Male	122(51.3%)	141(56.4%)	
Age (years $\pm$ SD)	55 $\pm$ 0.2	55.1 $\pm$ 0.4	1.0
Co-morbidities			0.81
Hypertension	45(18.9%)	37(14.7%)	
Diabetes Mellitus	19(8%)	25(10%)	
Obesity	3(1.3%)	4(1.6%)	
Hyper/hypothyroidism	6(2.5%)	6(2.4%)	
Ischaemic heart disease	4(1.7%)	8(3.2%)	
Asthma/chronic airway disease	7(2.9%)	6(2.4%)	
Hypercholesterolaemia	4(1.7%)	5(2%)	
Haematological disorders	3(1.3%)	0(0%)	
Neurological disorders	5(2.1%)	3(1.2%)	
Rheumatological disorders	6(3.9%)	3(1.2%)	
History of malignancies	1(0.4%)	2(0.8%)	
Psychiatric disorders	2(0.8%)	2(0.8%)	
Epilepsy	2(0.8%)	2(0.8%)	
History of transplant/immunosuppressive	0(0.0%)	2(0.8%)	

4.5.2 Procedure findings

There was no difference to the extent of examination between both arms ($p=0.62$). For the majority of the procedures, the endoscopists were able to reach the descending colon and beyond (control and intervention group, 88.2% and 90% respectively). Table 12 details the procedures and polyp data outcome of the study.

4.5.3 Polyp and adenoma detection rate

A total of 216 polyps detected in 489 participants, accounts for an overall polyp prevalence of 44.2% and 0.4 polyps per patient. The polyp detection rate (PDR) was significantly higher in the control arm when compared to intervention arm (34.9% and 26.8%, $p=0.05$). However, there was no difference in ADR between both groups ($p=0.91$). In addition, there was no difference in serrated polyp detection rate or advanced polyp detection. Mean number of polyps per patient was higher in the control arm but failed to reach statistically significant levels ($p=0.07$). There was no difference in mean number of adenomas, SSA/Ps or advanced adenomas per patient between both groups (Table 13 & 14)

Table 12. Procedural findings

	Control N=238	Intervention N=251	p value
Total procedure time (median & IQR)	9(9,10)	8.5(6,9)	0.11
Insertion time	3(2-4)	5(4,5)	<0.001
Withdrawal time	6(6,6)	3(3,4)	<0.001
Extent of examination – Number (%)	169(71%)	194(77.6%)	0.62
Descending colon	28(11.8%)	25(10%)	
Sigmoid colon	38(16%)	29(11.6%)	
Splenic flexure	3(1.2%)	2(0.8%)	
Transverse colon			
Polyp detection rate (%)	34.9	26.8	0.05
Hyperplastic polyps	11.4	6.8	0.08
SSA/Ps	1.7	3.2	0.38
Cancer	0	0.4	1.0
Adenoma detection rate (%)	16	16.4	0.91
Advanced adenoma detection rate (%)	2.5	4.4	0.33

Table 13. Mean number of polyps and adenoma per participants

	Control Mean± SD	Intervention Mean± SD	P value
Polyps	0.74 ± 2.48	0.48 ± 1.48	0.07
<5mm	0.66 ± 2.46	0.38 ± 1.42	0.06

6-9mm	0.06 ± 0.25	0.05 ± 0.29	0.45
≥10mm	0.03 ± 0.21	0.04 ± 0.19	0.1
Adenomas	0.19 ± 0.45	0.2 ± 0.49	0.89
<5mm	0.13 ± 0.38	0.14 ± 0.38	0.64
6-9mm	0.05 ± 0.24	0.04 ± 0.22	0.56
≥10mm	0.01 ± 0.09	0.03 ± 0.17	0.11
SSA/Ps	0.03 ± 0.34	0.05 ± 0.33	0.28
Hyperplastic polyps	0.13 ± 0.37	0.09 ± 0.36	0.08
Advanced adenomas	0.03 ± 0.16	0.05 ± 0.23	0.26

4.5.4 Procedure time

There was no significant difference in total procedure time ($p=0.11$). As predicted, the median insertion time in the intervention arm and withdrawal time in the control arm were prolonged by 2-3 minutes due to the requirements of study design.

4.5.5 Endoscopist based analysis

Adenoma detection rates were evaluated for each endoscopist separately to ascertain any significant difference between both arms. When five individual endoscopists data were analysed, no significant differences were found (Table 15).

Table 14. Endoscopist based analysis of ADR

Endoscopist number	Control % (n/N)	Intervention % (n/N)	P value
1	20.0% (14/70)	18.9% (14/74)	1.0
2	30.8% (4/13)	23.8% (5/21)	0.70
3	13.2% (7/53)	14.6% (8/55)	1.0
4	15.5% (11/71)	16.0% (12/75)	1.0
5	6.7% (2/30)	12.5% (3/24)	0.65

4.5.6 Comfort score

Comfort scores were graded for all procedures on a 5-point scale (0- comfortable and 4 – severe discomfort). Comfort scores were reported separately by the assisting endoscopy nurse and participants. There was no significant difference in comfort scores (Table 15) between control and intervention arms when reported by nurses ($p=0.36$) or by participants ($p=0.9$).

Table 15. Comfort score as reported by nursing assistant and participants

	Category	Control N (%)	Intervention N (%)	P-value
Comfort score – nurse	Comfortable	31 (13.0%)	35 (14.0%)	0.36
	Minimal	155 (65.2%)	169 (67.6%)	
	Mild	40 (16.8%)	38 (15.2%)	
	Moderate	12 (5.0%)	8 (3.2%)	
	Severe	0 (0.0%)	0 (0.0%)	
Comfort score – patient	Comfortable	49 (20.6%)	50 (20.1%)	0.90
	Minimal	99 (41.6%)	105 (42.2%)	
	Mild	65 (27.3%)	65 (26.1%)	
	Moderate	23 (9.7%)	28 (11.2%)	
	Severe	2 (0.8%)	1 (0.4%)	

4.5.7 Impact of Queue position on ADR

All bowel scope procedures were performed on an evening session of a working day (5-8pm). We assessed whether fatigue toward the end of the session could have an impact on ADR. When we analysed the correlation between ADR and queue position of the procedure within a dedicated screening list (Table 16), no difference in ADR was found. In fact, ADR was higher toward the end of the list when compared to the first half.

Table 16. Impact of Queue position on ADR

Queue position	ADR % (n/N)	Difference % (95% CI)	P-value
Position 1 – 4	14.3% (37/258)	0	0.22
Position 5 – 8	18.6% (37/199)	4.3% (-2.6%, 11.1%)	

4.6 Discussion

In the present randomised controlled study, we evaluated the impact of additional careful examination during scope insertion in a screening population undergoing flexible

sigmoidoscopy. Our findings showed that an additional inspection during insertion does not have an impact on ADR. Our findings do not support enhanced time taken to inspect the bowel during the insertion phase of the procedure.

Anecdotal evidence suggests that when small polyps (<10mm in size) are detected on insertion and not removed, they can be difficult to find again on scope withdrawal. Hence, in our practice, we routinely remove small polyps as and when they are detected. Hewett et al, described this phenomenon and argue that it could arise due to certain areas of the colon being better distended and visualised during insertion (175). Morini and colleagues described a prospective study of 378 patients with 396 adenomas and mentioned that nearly two third (249 adenomas) were detected during the insertion phase, suggesting detection during insertion is an important part of a quality colonoscopic examination (181). Wildi et al performed a randomised controlled trial in which 301 patients underwent polypectomy either during both insertion and withdrawal phases or just during the withdrawal phase. In the polypectomy only on withdrawal group, 13 polyps (3.3%) that had been seen on insertion could no longer be detected on withdrawal(178).

However, three other prospective randomised trials, failed to show any impact on ADR by performing an additional inspection during insertion(175,182-183). Recently Cheng et al. described a study where 421 patients were randomised either to receive inspection and polypectomy during both phases of the procedure (study arm), or inspection and polypectomy only in withdrawal (control arm). This study concluded that there was no significant difference in ADR (63.5% and 68.1%), or MAP (1.6 and 1.9) between groups (183). Our study findings were remarkably similar to the negative studies mentioned above. In our study 78(36.1%) polyps were detected during the insertion phase of the study while 128 were detected during withdrawal. As polypectomies were performed either during insertion or withdrawal at each

endoscopists discretion, we are unable to conclude that polyps detected on insertion would have been detected in the withdrawal phase as well.

The mean number of polyps per participant was significantly higher in our control arm. Several studies have showed that prolonged withdrawal times improve detection of adenomas and serrated polyps (162-163,184) and the 6 minutes withdrawal time in the control arm was longer than the usual 3 minutes. As endoscopists are accustomed to have a careful examination on withdrawal in the routine clinical practice could have contributed to this discrepancy. Endoscopists could have concentrated more during withdrawal rather than insertion and withdrawal phase of the examination.

Inspection during insertion of the colonoscope could lead to over inflation and lengthening of the colon potentially creating acute angulation, particularly at the mid sigmoid and sigmoid/descending junction. This could lead to a prolonged and more difficult insertion of the colonoscope(185). Also, after prolonged insertion, the endoscopist might feel fatigued and under time pressure which could result in a rapid withdrawal leading to a high miss rate. To abolish the impact of fatigue, we separately analysed the queue position of the procedure and the impact on ADR. A retrospective reviewed by Lee and colleagues assessed the impact of queue position in the endoscopic scheduling on colonoscopy. They reviewed 1083 colonoscopies performed by 28 endoscopists over a 4-month period. The study showed a 5.45% reduction in polyp detection with each increment in queue position($p=0.016$) (92). In our study we did not find any difference in ADR according to the queue position. Furthermore, WT in our study (median >4 mins) was well above the recommended threshold of 3 minutes for flexible sigmoidoscopy within the UK National bowel cancer screening programme. Therefore, queue position, which is an indirect marker of fatigue, did not influence performance in our study.

The strengths of this study are the randomised, controlled trial design with a large sample size. Also, our methodology is simple, practical, and reproducible and unlike other studies of a similar nature (performed only by experienced endoscopists), the procedures were performed by moderately experienced Endoscopy Fellows still in a gastroenterology training programme. Hence, the results are more generalizable to routine clinical practice. Our study had some limitations. Firstly, it was limited to a flexible sigmoidoscopy examination of left side of the colon and therefore the findings could not be generalized to colonoscopy practice. Secondly, it was a single centre study and included participants only in the age range of 55-59 years within the UK National Bowel Cancer Screening programme and therefore may be of less relevance to other countries that do not screen by flexible sigmoidoscopy. Finally, even though the participants were masked to the method of inspection during the procedure, masking the endoscopists was not possible. It is a common limitation for majority of endoscopic interventional studies.

In summary, the INWARD study suggests that additional careful inspection on insertion during screening flexible sigmoidoscopy does not increase ADR, mean number of adenomas or SSA/Ps per patient. Additional inspection during insertion was well tolerated but our findings do not support its introduction into clinical practice. Careful inspection during withdrawal remains the cornerstone of a quality examination.

Chapter 5

Endocuff-assisted colonoscopy vs Cap-assisted colonoscopy in adenoma detection: A randomised tandem study (Detection in Tandem Endocuff Cap Trial – DETECT)

5.1 Background and aims

Adenomas and other significant polyps can be missed during colonoscopy inspection even when the procedure is performed by experienced endoscopists(10) and the ADR has been shown to be an independent predictor of the risk of interval CRC post screening colonoscopy(11,170-171,186). Reasons for lesions not being detected at colonoscopy include; suboptimal technique; shorter withdrawal time; inadequate bowel preparation; presence of flat, depressed or subtle lesions; and the inability to visualize the proximal side of haustral folds or flexures(159,187). Optical imaging innovations and technological developments in the field of colonoscopy have attempted to decrease the adenoma miss rate with the introduction of high-definition endoscopes, electronic chromoendoscopy (such as narrow band imaging), wide-angle colonoscopes, retrograde viewing devices and adjunct disposable distal attachments(56,153). Views may also be improved with dynamic patient position changing and routine retroflexion(43,188).

Studies involving relatively simple, disposable distal attachment devices (Cap, Endocuff and Endorings) have shown benefits compared with standard colonoscopy (SC)(67-68,154,189-191). Several randomized controlled trials highlighted the impact of Endocuff on ADR including the largest ADENOMA trial with Endocuff Vision (Figure 14 &15). This study

showed an increment in ADR to 10% in a bowel cancer screening population(61-62,192). Cap assisted colonoscopy (Figure 16& 17) trials have been rather heterogenous and report mixed results to date(154,189-190) but the cap has also been reported to make insertion easier. Tandem studies in which each patient undergoes back to back colonoscopies on the same day, have been used to evaluate adenoma miss rate (AMR) between a new device or technology and conventional colonoscopy(28,169) and we employed a similar study design to compare the two most promising distal attachment devices to date; the Endocuff Vision™ (Arc Medical Design, Leeds, UK) and the straight plastic cap (disposable distal attachment, Olympus, Tokyo , Japan).



Figure 14. Endocuff Vision

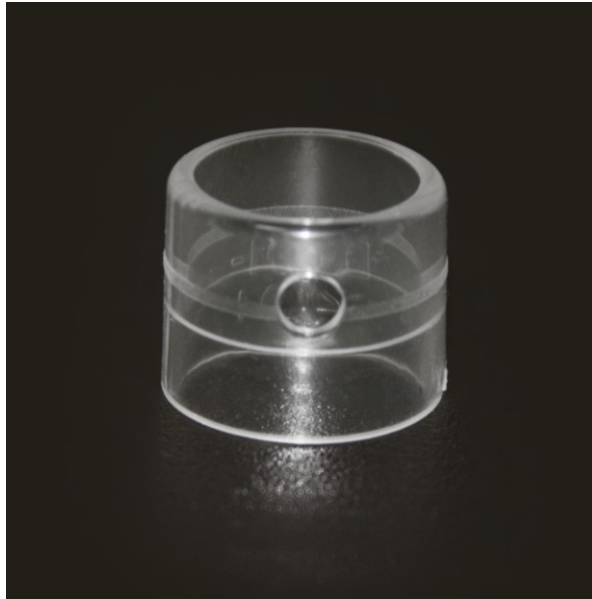


Figure 15. Transparent Cap

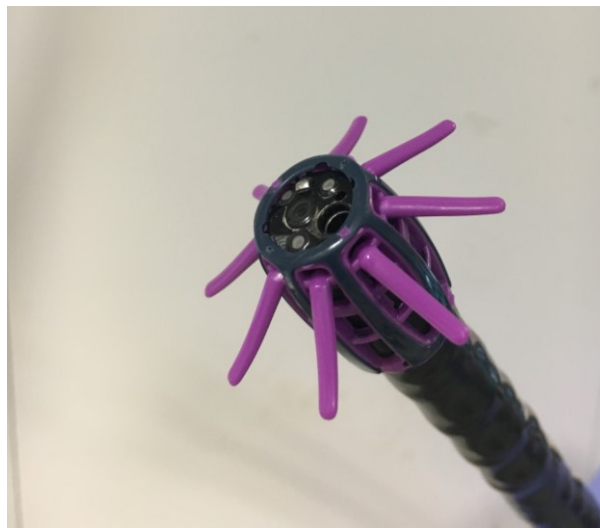


Figure 16. EV on a colonoscope



Figure 17. Cap on a colonoscope, 4mm length beyond the distal end

5.2 Methods

5.2.1 Study design

A prospective, randomized, tandem study was conducted between April 2016 and May 2017 in a single endoscopy unit in the United Kingdom. The DETECT trial protocol was reviewed and approved by the East of England (Cambridge) ethics committee on the 4th of January 2016 (Reference 15/EE/0415). The study was registered with clinical trial.gov NCT03254498 and International Standard Randomized Controlled Trials Number ISRCTN 58994883.

5.2.2 Participants

Patients older than 18 years and referred for a colonoscopic examination via the symptomatic pathway at our institution were invited to participate in the study. Patients with the following conditions or pathology were excluded: established or suspected of large bowel obstruction, known CRC or polyposis syndrome, previous diagnosis of colonic stricture or severe diverticular disease, active colitis, patients on anticoagulants or antiplatelets which could not be stopped pre procedure, attending an elective therapeutic procedure and pregnancy. Few (n=10) invited patients were not enrolled due to logistical reasons or procedure cancellation.

5.2.3 Endoscopists

Three experienced endoscopists who had performed more than 1500 colonoscopies and who had experience in using Cap and EV (>20 cases for each device) participated in this trial. All endoscopists were senior Gastrointestinal (GI) fellows who were certified by the Joint Advisory Group on GI Endoscopy UK to perform colonoscopy procedures and polypectomies independently.

5.2.4 Colonoscopy procedures

All patients had a standard bowel preparation either with Senna (10 tablets) and 2 sachets of magnesium citrate (Citramag; Sanochemia Diagnostics UK Ltd, Bristol, UK) or 2 sachets of MoviprepTM (Macrogol and ascorbic acid; Norgine, UK). Patients with sub optimal bowel preparation were cleaned using copious amount of water to achieve adequate mucosal inspection. Patients with poor bowel preparation (semi solid stools that could not be suctioned or washed away) were excluded. High-definition Olympus CF-H260DL, PCF-H290ZL/I or CF-H290I/L colonoscopes with Lucera video processors (Olympus, Tokyo, Japan) were used for all procedures. When polyps were detected, either they were biopsied or resected and the samples were sent for histopathology.

5.2.5 Randomisation

A computer-generated randomised sequence was used to assign patients to undergo tandem colonoscopies with either Cap assisted colonoscopy (CAC) or EAC being performed first. A concealed envelope containing the randomization sequence was opened only after informed written consent was taken. The first procedure was followed immediately by the second device-assisted colonoscopy and was performed by the same endoscopist.

5.2.6 Outcomes

The primary aim was to compare adenoma detection rates (ADR) between EAC and CAC.

Secondary outcome measures were:

1. To compare the Mean number of Adenomas per procedure (MAP) between EAC and CAC
2. To ascertain the miss rates for polyps, adenomas, advanced adenomas, Sessile serrated adenomas/polyps (SSA/P) and CRC
3. To compare the caecal intubation time (CIT) and WT between EAC and CAC.
4. To demonstrate any difference in comfort score including degree of discomfort on anal intubation.
5. To compare the number of dynamic position changes (DPC) needed to achieve a satisfactory mucosal view between EAC and CAC.

Patient comfort score was assessed by a validated nurse assessment tool (1- completely comfortable, 2- minimal discomfort, 3- mild discomfort, 4- moderate discomfort, 5- severe discomfort) and patient questionnaires. Patients were followed up for 21 days post procedure and any adverse events were collected and reported.

5.2.7 Statistical analysis

5.2.7.1 *Sample size calculation*

The study was powered to detect a difference in the ADR (primary outcome) between EAC and CAC. Preliminary work performed by the chief Investigator suggested that a 10% increase in ADR is possible with EV when compared to Standard colonoscopy (SC). Recent meta-analysis of CAC vs SC showed no difference in ADR. We hypothesized that the performance of CAC would be remarkably similar to SC. A 10% difference in ADR was considered clinically significant. ADR for symptomatic patients who underwent a colonoscopy at our

institution was 16% (unpublished data). Therefore, to demonstrate a 10% difference in ADR with a 5% significance level and 90% power using a two-sided test, the sample size was calculated as 154 patients per group.

5.2.7.2 *Analysis*

The demographic and baseline variables were summarized descriptively for the two study arms separately. No formal hypothesis tests were used to compare the two groups for these measures. All efficacy analyses were compared between the two groups, for each procedure separately.

Continuous variables were summarized median or mean and standard deviation/ inter-quartile range. The exception to these rules was for MAP and other polyp/adenoma detection outcomes and miss rates which were summarized as mean/standard deviation, regardless of the data distribution. Categorical variables were summarised by the frequency and percentage of values in each category.

The primary outcome, ADR was calculated using Chi- square test. Two-sided p-values were reported, along with 95% confidence intervals for the mean difference between groups.

All secondary outcome analyses were performed for data from the first and second procedure separately. For each procedure, chi-square test was used to compare this outcome between groups. Several secondary outcomes including AMR were analysed using the Mann-Whitney test. The number of position changes were found to be approximately normally distributed, and s unpaired t-test was used to compare between groups for each procedure.

5.3 Results

5.3.1 Participants and procedures

A total of 318 patients were invited to participate in the study. 164 patients were excluded as they either did not meet the inclusion criteria (56%) or declined to undergo tandem colonoscopies on the same day (24%). We recruited 154 patients (mean age 61.4 ± 13.6) with

equal sex distribution (males 51%) and the trial flow chart is illustrated in figure 18. Main indications for a colonoscopy were adenoma surveillance (28%), recent change in bowel habits (21%), family history of CRC (16%) and rectal bleeding (10%). No patients were lost to follow up. Patient characteristics are summarized in table 18.

All procedures were complete to the caecum during CAC. However, during EAC, 6.6% (10/152) colonoscopies were not completed. Five procedures during the first pass and the reasons were moderate discomfort, severe diverticulosis with fixed and angulated sigmoid colon. During the 2nd pass five procedures were not completed with the Endocuff as two patients refused to undergo the 2nd examination and in three cases a fixed and angulated sigmoid colon could not be negotiated. All patients were included in the analysis and followed up for 21 days as per protocol.

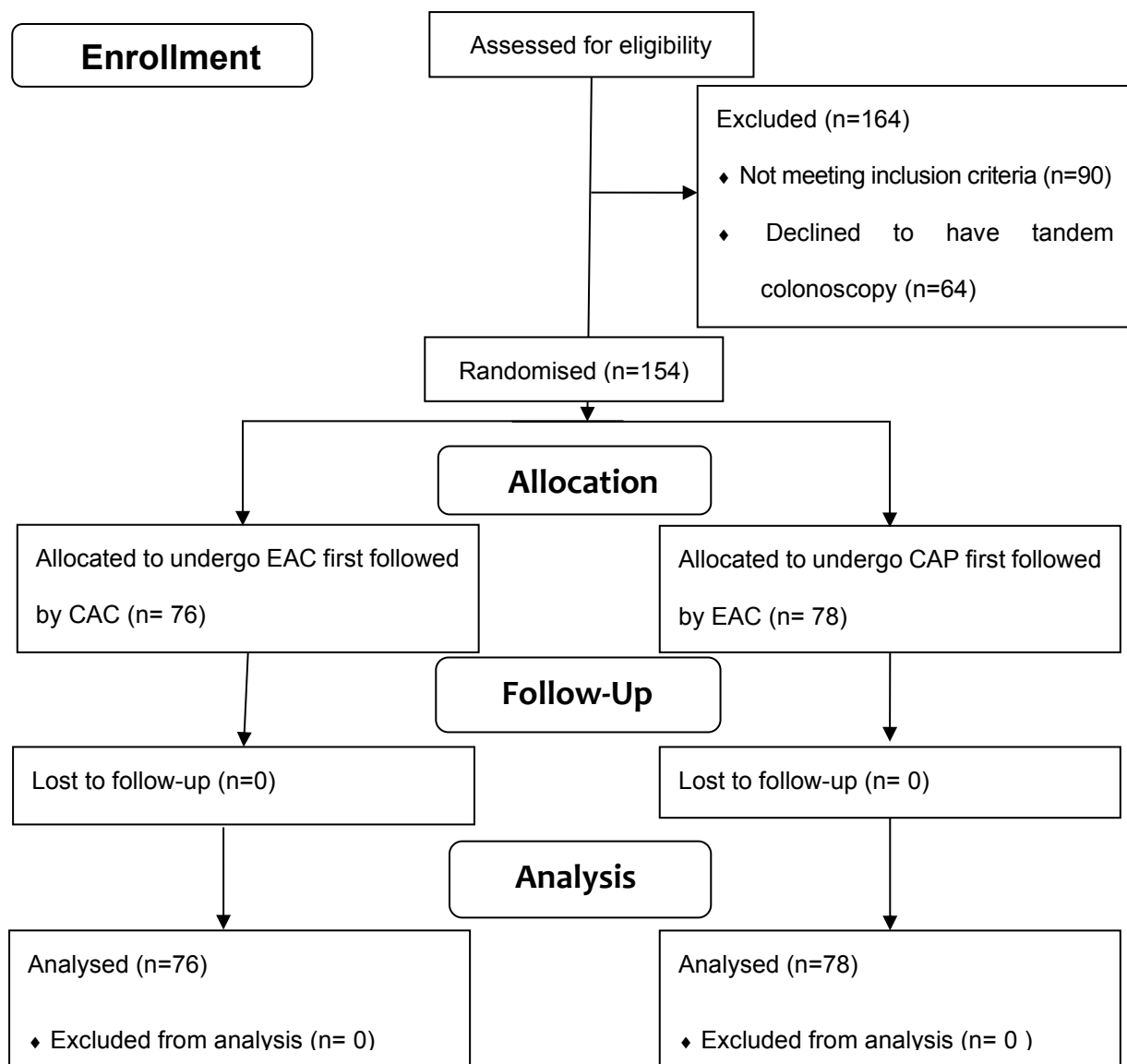


Figure 18. CONSORT study design

Table 17. Patient characteristics

	Both groups (n=154) No (%)	CAC first (n=78) No (%)	EAC first (n=76) No (%)	P value
Sex				
Male	79 (51.3%)	43 (55.1%)	36 (47.4%)	0.54
Female	75 (48.7%)	35 (44.9%)	40 (52.6%)	0.61
Age – Mean (SD) years				
BMI < 20	15 (9.9%)	11 (14.3%)	4 (5.3%)	0.04
20-30	93 (61.2%)	48 (62.3%)	45 (60.0%)	0.72

	Both groups (n=154) No (%)	CAC first (n=78) No (%)	EAC first (n=76) No (%)	P value
> 30	44 (29.0%)	18 (23.4%)	26 (34.7%)	0.32
Indication (*)				
PR Bleeding	15 (9.7%)	10 (12.8%)	5 (6.6%)	0.08
CIBH	32 (20.8%)	17 (21.8%)	15 (19.7%)	0.62
PR Bleeding + CIBH	7 (4.6%)	3 (3.9%)	4 (5.3%)	0.45
Family history CRC	25 (16.2%)	13 (16.7%)	12 (15.8%)	0.86
Polyp surveillance	43 (27.9%)	18 (23.1%)	25 (32.9%)	0.12
IDA	11 (7.1%)	8 (10.3%)	3 (4.0%)	0.1
FH of CRC + polyp surveillance	12 (7.8%)	6 (7.7%)	6 (7.9%)	0.94
Post CRC surveillance	10 (6.5%)	5 (6.4%)	5 (6.5%)	0.96
Abdominal pain + CIBH	8 (5.2%)	4 (5.1%)	4 (5.2%)	0.95
Colitis surveillance	8 (5.2%)	4 (5.1%)	4 (5.3%)	0.95
Weight loss	6 (3.9%)	4 (5.1%)	2 (2.6%)	0.34

(*) One patient may have multiple indications

5.3.2 Primary outcome – ADR

When we compared the first pass with EV or Cap, there was a significantly higher ADR in the EAC arm ($p=0.001$). The results showed that at least one adenoma was detected in 26% of patients in the CAC group, compared to 53% in the EAC group. This gives a difference in ADR of 27% between groups. An incredibly significant difference was also found when considering data from the second procedure, where the ADR was 9% in CAC group compared to 29% in EAC group (table 18). Adenomas prevalence by size and location were displayed in table 19.

Table 18. Comparison of Adenoma Detection Rate between both arms

Procedure	Adenomas detected (Yes/No)	CAC No (%)	EAC No (%)	% Difference (95% CI)	P value
1	No	58 (74.4%)	36 (47.4%)		
	Yes	20 (25.6%)	40 (52.6%)	27.0% (12.1%, 41.8%)	0.001
2	No	69 (90.8%)	55 (71.4%)		
	Yes	7 (9.2%)	22 (28.6%)	19.4% (7.4%, 31.4%)	0.002

Table 19. Prevalence of adenomas per size and location

	CAC (n=78)	EAC (n=76)	% Difference (95% CI)	P-value
≤5 mm	12 (15.4%)	32 (42.1%)	26.7% (13.0%, 40.4%)	<0.001
6-9 mm	13 (16.7%)	17 (22.4%)	5.7% (-6.8%, 18.2%)	0.37
10+ mm	3 (3.9%)	13 (17.1%)	13.3% (3.8%, 22.7%)	0.007
Rectum	1 (1.3%)	4 (5.3%)	4.0% (-1.6%, 9.6%)	0.16
Sigmoid Colon	8 (10.3%)	18 (23.7%)	13.4% (1.7%, 25.1%)	0.03
Descending Colon	3 (3.9%)	6 (7.9%)	4.0% (-3.3%, 11.4%)	0.28
Splenic Flexure	2 (2.6%)	7 (9.2%)	6.6% (-0.7%, 14.0%)	0.08
Transverse Colon	7 (9.0%)	10 (13.2%)	4.2% (-5.7%, 14.1%)	0.41
Hepatic Flexure	2 (2.6%)	15 (19.7%)	17.2% (7.6%, 26.7%)	<0.001
Ascending Colon	3 (3.9%)	9 (11.8%)	8.0% (-0.4%, 16.4%)	0.06
Caecum	6 (7.7%)	9 (11.8%)	4.1% (-5.2%, 13.5%)	0.39

5.3.3 Secondary outcomes

5.3.3.1 AMR

The AMR was significantly lower in EAC (6%) when compared to CAC (19%, [p=0.002]). A more pronounced effect was noted for diminutive (<5mm) adenomas, 1.8% for EAC and 19.6% for CAC. There was no statistically significant difference in SSA/P or advanced adenoma miss rate (table 20).

Table 20. Comparison of Adenoma Miss Rate in tandem colonoscopy

Polyps histology and size	CAC (n=78)	EAC (n=76)	Mean difference (95% CI)	P value
Adenomas (any size)	19.0 %	6.0 %	-13.0 (-22.1, -3.8)	0.002
Adenoma ≤5 mm	19.6 %	1.8%	-17.8 (-26.5, -9.1)	<0.001
Adenoma 6-9 mm	2.9 %	3.7 %	0.9 (-4.4, 6.2)	0.69
Adenoma >10mm	2.6 %	1.6 %	1.0 (-3.5, 5.5)	0.98
Polyps (any size)	26.1%	8.4 %	-17.7 (-27.3, -8.0)	<0.001
Polyps ≤5 mm	24.4 %	4.3 %	-20.2 (-29.2, -11.1)	<0.001
Polyps 6-9 mm	3.7 %	6.1 %	-2.4 (-8.8, 4.1)	0.52
Polyps >10 mm	2.6 %	0.8 %	1.9 (-1.9, 5.7)	0.97
Cancer	0.0 %	0.0 %	(*)	
Advanced adenoma	4.2 %	4.6 %	0.4 (-6.0, 6.8)	0.98
SSA/P	4.9 %	1.8 %	-3.1 (-8.3, 2.1)	0.25

(*) No hypothesis test performed due to no missed cancers

5.3.3.2 *Total number of polyps/adenomas and mean number of polyps/adenomas per procedure*

When we analysed the findings of the first procedure the MAP was significantly higher ($p<0.001$) in EAC compared to CAC. MAP was 0.6 in the CAC arm, rising to 1.5 in the EAC arm, with a mean difference of 0.8 between groups (table 21).

There were significant differences between EAC and CAC in terms of the detection of diminutive adenomas (≤ 5 mm) and larger adenomas (>10 mm), but no difference was found for small adenomas (6-9mm). Detection of diminutive adenomas was 42% in the EAC group, but only 15% in the CAC group ($p<0.001$). Detection of large adenomas was 17% in the EAC group, but only 4% in the CAC group ($p=0.007$). There was no significant difference in the number of small adenomas between both groups ($p=0.37$).

Table 21. Mean Number of polyps/adenomas per patient – 1st & 2nd procedure

Polyp histology and size	CAC (n=78) Mean (SD)	EAC (n=76) Mean (SD)	Mean difference (95% CI)	P-value
First procedure				
Adenomas (any size)	0.64 (1.77)	1.46 (2.65)	0.82 (0.10, 1.54)	<0.001
Adenoma ≤5 mm	0.32 (0.95)	0.75 (1.41)	0.43 (0.05, 0.81)	<0.001
Adenoma 6-9 mm	0.24 (0.67)	0.34 (0.78)	0.10 (-0.13, 0.33)	0.36
Adenoma 10+ mm	0.06 (0.37)	0.37 (1.33)	0.30 (0.00, 0.61)	0.007
Polyps (any size)	1.17 (1.99)	2.13 (3.28)	0.96 (0.10, 1.83)	0.007
Polyps ≤5 mm	0.64 (1.14)	1.25 (1.78)	0.61 (0.13, 1.08)	0.01
Polyps 6-9 mm	0.38 (0.84)	0.42 (0.87)	0.04 (-0.24, 0.31)	0.76
Polyps 10+ mm	0.13 (0.47)	0.46 (1.46)	0.33 (-0.01, 0.68)	0.03
Advanced adenoma	0.09 (0.49)	0.49 (1.48)	0.40 (0.05, 0.75)	0.001
SSP	0.10 (0.35)	0.16 (0.57)	0.06 (-0.09, 0.20)	0.91
Second procedure				
Adenomas (any size)	0.13(0.47)	0.45 (0.88)	0.32 (0.10, 0.55)	0.002
Adenoma ≤5mm	0.04(0.26)	0.39 (0.78)	0.35 (0.16, 0.54)	<0.001
Adenoma 6-9mm	0.05(0.22)	0.04 (0.19)	-0.01 (-0.08, 0.05)	0.69
Adenoma 10+mm	0.03(0.16)	0.03 (0.16)	0.00 (-0.05, 0.05)	0.99
Polyps (any size)	0.18(0.51)	0.81 (1.34)	0.62 (0.30, 0.95)	<0.001
Polyps ≤ 5mm	0.09(0.33)	0.70 (1.28)	0.61 (0.31, 0.91)	<0.001
Polyps 6-9mm	0.05(0.22)	0.08 (0.27)	0.03 (-0.05, 0.10)	0.53
Polyps10+mm	0.03(0.16)	0.03 (0.16)	0.00 (-0.05, 0.05)	0.99
Advanced adenoma	0.07(0.30)	0.06 (0.30)	-0.01 (-0.10, 0.09)	0.98
SSP	0.03(0.16)	0.12 (0.49)	0.09 (-0.03, 0.21)	0.24

There was a significantly higher detection rate in EAC group (21%) compared to only 4% in the CAC group (p=0.001) for advanced adenomas (adenomas >10mm, villous histology or high-grade dysplasia). There was no significant difference in the detections of SSA/Ps between both arms (p=0.96). CRC was rare and detected only three patients. A remarkably similar trend was observed during the 2nd procedure. These findings were summarized in table 22.

Table 22. Adenoma/Polyp characteristics per patient – 1st & 2nd Procedure

Polyp histology and size	CAC (n=78)	EAC (n=76)	% Difference (95% CI)	P-value
First procedure				
Adenoma ≤5 mm	12 (15.4%)	32 (42.1%)	26.7% (13.0%, 40.4%)	<0.001
Adenoma 6-9 mm	13 (16.7%)	17 (22.4%)	5.7% (-6.8%, 18.2%)	0.37
Adenoma 10+ mm	3 (3.9%)	13 (17.1%)	13.3% (3.8%, 22.7%)	0.007
Polyps ≤5 mm	31 (39.7%)	41 (54.0%)	14.2% (-1.4%, 29.8%)	0.08
Polyps 6-9 mm	19 (24.4%)	20 (26.3%)	2.0% (-11.8%, 15.7%)	0.78
Polyps 10+ mm	7 (9.0%)	16 (21.1%)	12.1% (0.9%, 23.2%)	0.04
Cancer	2 (2.6%)	1 (1.3%)	(*)	
Advanced adenoma	3 (3.9%)	16 (21.1%)	17.2% (7.1%, 27.3%)	0.001
SSP	7 (9.0%)	7 (9.2%)	0.2% (-8.8%, 9.3%)	0.96
Second procedure				
Adenoma <5mm	2(2.6%)	20(26%)	23.3% (12.9%, 33.8%)	<0.001
Adenoma 6-9mm	4(5.3%)	3(3.9%)	-1.4% (-8.0%, 5.2%)	0.69
Adenoma 10+mm	2(2.6%)	2(2.6%)	0.0% (-5.1%, 5.0%)	0.99
Polyps <5mm	6(7.9%)	28(36.4%)	28.5% (16.1%, 40.8%)	<0.001
Polyps 6-9mm	4(5.3%)	6(7.8%)	2.5% (-5.3%, 10.3%)	0.53
Polyps 10+mm	2(2.6%)	2(2.6%)	0.0% (-5.1%, 5.0%)	0.99
Cancer	0(0.0%)	0(0.0%)	(*)	
Advanced adenoma	4(5.3%)	4(5.2%)	-0.1% (-7.1%, 7.0%)	0.99
SSA/P	2(2.6%)	5(6.5%)	3.9% (-2.7%, 10.4%)	0.25

(*) No hypothesis test performed due to small number of findings

5.3.3.3 *Caecal intubation and withdrawal times*

Caecal intubation rate was 100% in CAC when compared to 94.7% in EAC group. This is due to the fact that in 10 patients (1st and 2nd procedures combined) the Endocuff was removed to complete the examination. The results suggested that during both procedures, caecal intubation time (CIT) were lower in the EAC group compared to CAC (table 23). CIT was a median of 1 minute shorter in the EAC group during the first procedure (p=0.01), and a median of 2 minutes shorter in the second procedure (p=0.05).

Table 23. Comparison of caecal intubation and withdrawal times

Procedure time	CAC (mins) Median (IQR)	EAC (mins) Median (IQR)	Difference [95% CI]	P-value
Caecal intubation time - 1 st	7 [5, 10]	6 [4, 8]	-1 [-2, 0]	0.01
Caecal intubation time - 2 nd	6 [4, 7]	4 [3, 6]	-2 [-1, 0]	0.005
Withdrawal time - 1 st	8 [6, 11]	10 [7, 15]	2 [0, 3]	0.01
Withdrawal time - 2 nd	6 [5, 7]	6 [5, 8]	0 [0, 1]	0.40
Negative withdrawal time - 1 st	6 [5, 8]	6 [6, 7]	0 [0, 1]	0.47
Negative withdrawal time - 2 nd	6 [5, 7]	5 [4, 6]	-1 [-1, 0]	0.07

Conversely, withdrawal time (WT) was significantly longer in the EAC group in the first procedure ($p=0.01$) The median difference was 2 minutes between groups. However, there was no significant difference in WT during the second procedure ($p=0.47$). When negative WT was analysed (patients where no polyps were detected or resected), there were no significant differences between the two groups during the first or second procedures (median of 6 mins each, $p=0.37$).

5.3.3.4 *Dynamic position changes (DPC) and patient experience*

Number of DPC during insertion and withdrawal were compared between groups, with the results summarised in table 24. During insertion, there were significantly fewer changes in the EAC group ($p<0.04$) for the first procedure. The mean number of changes was 2.3 in the CAC group, compared to 2.0 in the EAC group. There was no significant difference in DPC when performing colonoscopic insertion during the second procedure ($p=0.47$). The number of DPC during withdrawal was significantly lower in the EAC group for both the first ($p<0.001$) and second procedure ($p<0.001$). The number of changes were reduced in the EAC group by 0.9 per patient for the first procedure, and 1.0 per patient for the second procedure.

Table 24. Comparison of number of dynamic position changes during insertion and withdrawal

Phase of colonoscopy - Procedure	CAC Mean (SD)	EAC Mean (SD)	Difference (95% CI)	P-value
Insertion – 1 st	2.3 (0.9)	2.0 (0.7)	-0.3 (-0.5, -0.1)	0.04
Insertion – 2 nd	2.1 (0.7)	2.0 (0.6)	-0.1 (-0.3, 0.1)	0.47
Withdrawal – 1 st	3.3 (0.8)	2.4 (0.7)	-0.9 (-1.1, -0.6)	<0.001
Withdrawal – 2 nd	3.1 (0.8)	2.2 (0.6)	-1.0 (-1.2, -0.7)	<0.001

Overall, patients tolerated tandem colonoscopic procedures with two different devices very well. 94% of patients in EAC group and 91% of patients in CAC group had a “completely comfortable examination” or just “minimal discomfort” during the procedure (table 25). 6.4% of patients in EAC and 4% in CAC group reported mild to moderate discomfort while anal intubation. There were no adverse events reported either during the procedure or within the 21-day follow up period.

Table 25. Patient experience of discomfort during tandem colonoscopy

Patient experience	Category	CAC N (%)	EAC N (%)	P-value
Anal discomfort – 1 st procedure	Comfortable	67 (85.9%)	29 (39.2%)	<0.001
	Minimal	8 (10.3%)	51 (55.4%)	
	Mild	1 (1.3%)	4 (5.4%)	
	Moderate	2 (2.6%)	0 (0.0%)	
Anal discomfort – 2 nd procedure	Comfortable	66 (89.2%)	26 (35.6%)	<0.001
	Minimal	8 (10.8%)	44 (60.3%)	
	Mild	0 (0.0%)	2 (2.7%)	
	Moderate	0 (0.0%)	1 (1.4%)	
Discomfort score – 1 st procedure	Comfortable	19 (24.7%)	17 (23.3%)	0.86
	Minimal	51 (66.2%)	52 (71.2%)	
	Mild	6 (7.8%)	3 (4.1%)	
	Moderate	1 (1.3%)	1 (1.4%)	
Discomfort score	Comfortable	21 (28.4%)	13 (18.6%)	0.17

Patient experience	Category	CAC N (%)	EAC N (%)	P-value
– 2 nd procedure	Minimal	49 (66.2%)	52 (74.3%)	
	Mild	4 (5.4%)	5 (4.1%)	
	Moderate	0 (0.0%)	0 (0.0%)	

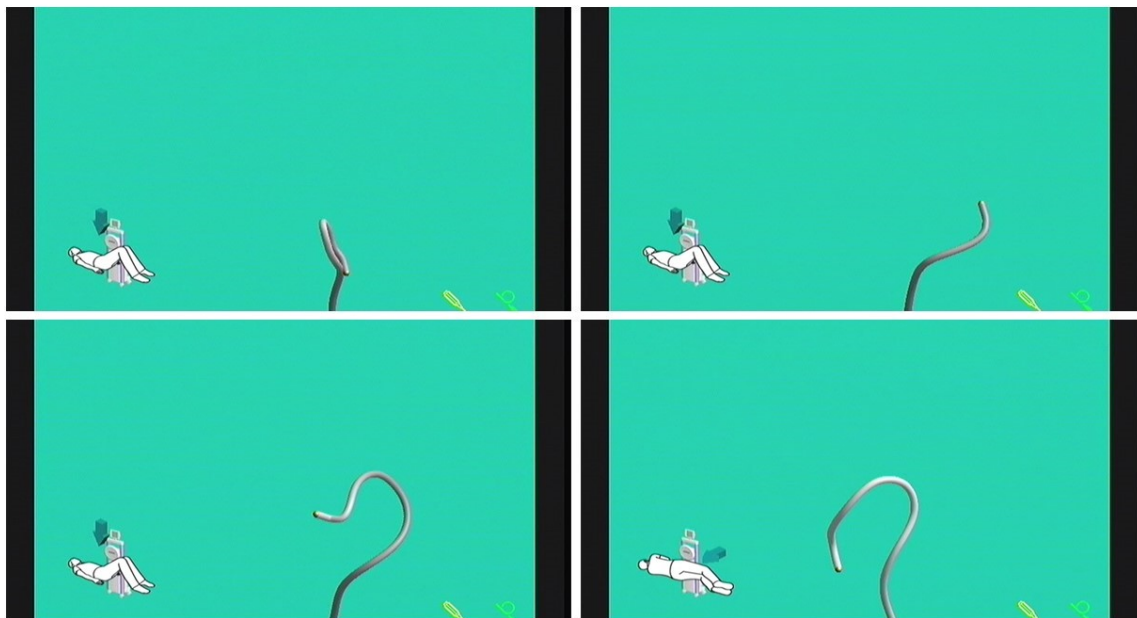


Figure 19. EAC Scope guide view

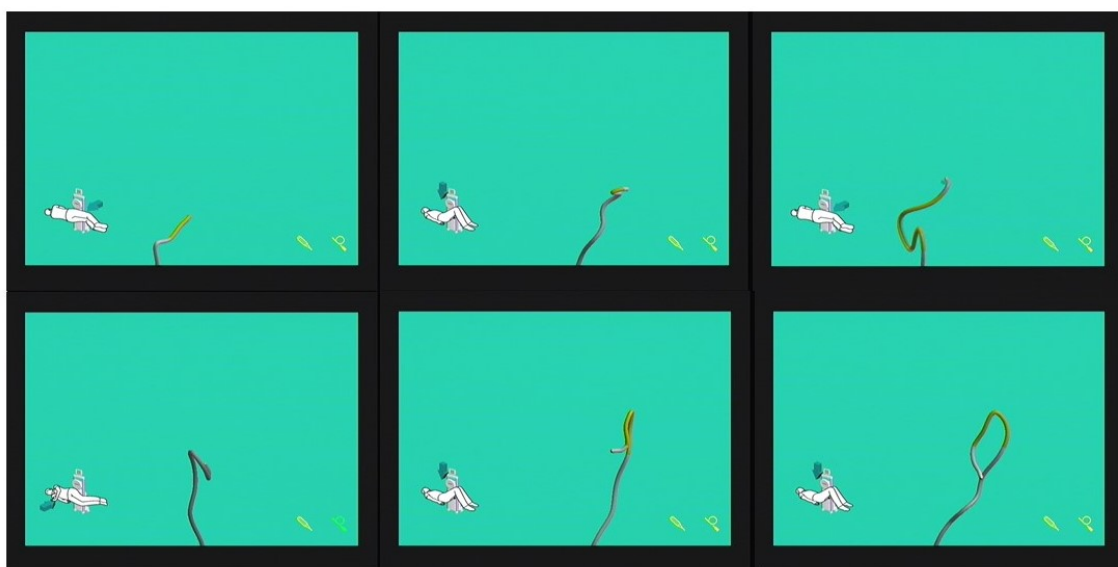


Figure 20. CAC scope guide view

5.4 Discussion

This is the first tandem, cross over, randomised trial to examine EAC with CAC. The primary aim was to compare ADR and our results highlighted that EAC significantly improved detection of adenomas by 27% compared to CAC ($p=0.001$). Total number of adenomas detected by EAC were significantly higher than that detected by CAC (153 vs 58, $p<0.001$). Furthermore, EAC improved the detection of missed adenomas by 13% (EAC 6% and CAC 19%) and SSA/Ps by 3% compared to CAC. Our findings were consistent with the miss rate of other tandem studies comparing CAC against SC. A study performed by Hewett et al, recruited 100 patients and the reported adenoma miss rate for CAC was 21%(193). The clinical significance of the significant improved detection of diminutive polyps and adenomas ($<5\text{mm}$) with EAC is unknown due the low malignant potential of these lesions, however improved detection of such polyps potentially parallels an improvement in larger polyp detection with EAC. Our study did not show lower miss rates for advanced adenomas($p=0.98$) but detection of adenomas bigger than 5mm($p=0.69$) and SSA/Ps ($p=0.25$) did improve. However, the rate failed to reach statistical significance.

Initial studies performed in Asia showed improved caecal intubation rates, intubation times and ADR with CAC when compared to SC(189,194-195). However, a recent study described by Pohl et al, randomized 1113 patients to undergo CAC and SC and this showed no difference in ADR (42% vs 40%; $p=0.452$)(155).

In contrast to the CAC studies, most trials evaluating the original Endocuff and EV against SC have showed significant improvements in ADR. An initial pilot study using EV showed a 16% improvement in ADR in a screening population(59). The ADENOMA study randomized 1772 patients to undergo EAC and SC showed a 10.8% increment in ADR in a bowel cancer screening population(60).

This study has showed a 27% increment in ADR for EAC when compared to CAC. For an ADR calculation we compared the first procedures of EAC and CAC. This level (27%) of ADR increase is significantly higher than previously described EAC studies. These higher rates might represent improved performance in a trial setting. Another potential explanation for this disparity could be due to the genuinely improved performance by EV in less experienced endoscopists as the interventionalists were GI fellows in training who had performed just over 1500 colonoscopies.

A recent meta-analysis of CAC and SC analysed 23 RCTs and 12 947 patients reporting a significantly shorter CIT (median of 0.82 min; 95%CI -1.20 to -0.44; $p < 0.01$) (196). Similarly, studies using EV showed a shorter CIT. Initial pilot and ADENOMA studies both showed a median reduction of 1 min when compared to SC (59-60, 197). Our study reported significantly quicker CIT for both devices when compared to other studies utilizing cap and Endocuff (median 6 min and 7 min) EAC and CAC respectively. CIT for EAC was significantly shorter than CAC (median difference 1 min, $p = 0.01$).

The difference could be due to easy manoeuvrability of the single set of softer and longer projections of EV and the ability to stabilize the scope tip during scope straightening manoeuvres especially in long, capacious and mobile colon (figure 19 & 20). In addition, the number of dynamic position changes needed to reach the caecum was far less than the standard colonoscopy.

Withdrawal time for EAC was slightly prolonged compared to CAC for the first procedure (median 2 min; $p = 0.01$) but equivalent for both groups during second procedure. In our study we measured the total withdrawal time (time spent on inspection + polypectomy time). One might argue that prolonged WT associated with increased ADR in EAC. we conducted a subgroup analysis of WT in which one or more polyps were resected. It showed no difference in WT (EAC vs CAC 10.5 vs 11 minutes, $p = 0.12$). Furthermore, in procedures where no polyps

were detected the WT were similar (EAC vs CAC 6 minutes each). The primary reason for this difference is probably that significantly more polyps were detected and resected when the procedure was performed with EV (total number of polyps resected were 83 and 52 for EAC and CAC respectively). This is a significant finding and shows the efficiency of the EV when performing a diagnostic and therapeutic procedures. Firstly, EV helps to improve the mucosal examination by holding back and everting the haustral folds, allows the endoscopist to visualize the proximal side of the folds, which helps to improve the polyp detection(60). Secondly, the finger like projections help to withdraw the colonoscope in a controlled manner and prevents rapid slippage of the scope, hence minimize the need for repeated 'to and fro' movements to completely visualize the mucosa especially at the flexures. Finally, EV provides a stable platform to perform multiple polypectomies and retrieval of polyp fragments, making the process time efficient(197). This observation was documented in multiple recent Endocuff studies(59-60,64-65,198) .

Another example of improved efficiency of EV was evident from the smaller number of dynamic position changes that were needed during insertion and withdrawal to complete the examination; insertion (median 2 and 2.3; $p=0.04$) and withdrawal (2.4 and 3.3; $p<0.001$ for EAC and CAC respectively). When colonoscopy is performed under deep sedation, it would be greatly beneficial as multiple position changes are cumbersome.

Efficiency of an intervention or device cannot be correctly measured by routine key performance indicators such as ADR, caecal intubation rate and WT. Therefore, there is a compelling need to develop an efficiency marker.

When compared to previous studies mucosal abrasions or undocking of the devices were not noted in this study(61-63). This could be due to improved design of EV compared to the original Endocuff with 2 rows of finger like projections.

One of the disadvantages of EAC in our study was that a small number of incomplete procedures were incomplete and EV had to be removed to complete the procedure. Ten out of 152 procedures (6.2%) were not completed due to inability to negotiate a fixed or angulated sigmoid colon or due to discomfort. EV had to be removed to complete the examination. This observation was noted in four recent trials of Endocuff and the cuff removal rate was similar to our study (4-6.4%)(60,65,196-197). The potential reasons for this inability to negotiate is probably secondary to the increase in the tip diameter of the colonoscope by 1-2mm by addition of EV and possibly more frictional resistance at the colonoscope tip in a narrowed or angulated colon. Conversely CIR was 100% in CAC and It appears that the cap design (soft plastic material and slight projection beyond the distal end of the scope) does not impede insertion through a fixed or angulated sigmoid colon and may even be advantageous providing enhanced vision in a narrowed lumen when all air is suctioned by keeping the mucosal folds away from the colonoscope tip.

Overall patient experience was similar in both groups and the vast majority (>94%.) tolerated the procedures very well regardless of the device used. With regards to anal discomfort on insertion, patients reported EAC was slightly more uncomfortable than CAC. When a colonoscopy is performed under mild, conscious sedation or no sedation, endoscopists should be aware of this issue and apply adequate lubrication and advocate gentle insertion technique.

Ileal intubation was not routinely attempted during this study. Our impression is that EV does not hinder distal terminal ileal (TI) intubation. However, deep ileal intubation was rarely possible with EV. Conversely, CAC appears to help passage into the TI and deep ileal intubation.

The strengths of this study are its tandem, cross over study design, in which the same endoscopist performed both procedures one after another. In addition, all demographic and procedure variables were equivalent between both groups. Almost all previous studies

comparing adjunct devices with standard colonoscopy have been performed by very experienced endoscopists. In our study participating endoscopists were moderately experienced endoscopists still in a gastroenterology training program so results may be more generalizable to average clinical practice.

One previous randomized study of EV vs standard colonoscopy (E-CAP) where 4 highly experienced colonoscopists performed all procedures, did not show any advantage in ADR with EV(197), however the larger ADENOMA randomized trial did show an advantage for EV). In the latter trial majority of colonoscopists were very experienced(60). However, in our study, the procedures were performed by moderately experienced colonoscopists, which may confirm that the benefit of EV is seen both in trainees and experienced colonoscopists.

The study limitations are it is a single centre study involving only three endoscopists and the endoscopists were not blinded for the device in use. This is a common and a consistent limitation with all endoscopic studies evaluating devices and novel technologies where blinding is not possible.

In summary, the DETECT study demonstrated that EV surpassed the performance of Cap by significantly reducing the adenoma miss rates in the hands of moderately experienced endoscopists albeit at the cost of the EV needing to be removed in a small minority of technically difficult colonoscopies.

Chapter 6

Number of significant polyps detected per six-minute withdrawal time at colonoscopy (SP6): A new measure of colonoscopy

6.1 Background and aims

Quality assessment of the colon consists of detailed, systematic, and meticulous inspection of the entire colonic mucosa. A thorough and careful mucosal inspection is essential to prevent CRC and cancer related mortality(199). The detection and resection of precancerous polyps is the primary goal of screening colonoscopy. Recently, there has been a focus on quality and safety of colonoscopy. Worldwide the demand for colonoscopy is increasing and with a limited workforce efficient working is of paramount importance(200).

6.1.1 Quest for a colonoscopy efficiency marker

We performed an extensive search in the literature for the definition of colonoscopic efficiency (CE), however no clear definition was found. We propose the following working definition as ‘the ability to detect clinically significant pathologies within acceptable time limits without compromising the quality or safety of the examination’.

CE is augmented by the following factors: optimal bowel preparation, technical ease of the procedure, technique of the endoscopist, high definition and high-quality video imaging and uninterrupted panoramic view of mucosal surface.

Although mucosal views may be improved with dynamic position changes and routine retroflexion in the rectum, these manoeuvres may not be effective in narrower colonic segments and flexures(43).

Recent technological developments in the field of colonoscopy such as wide-angle view colonoscopes and disposable distal attachments (EVTM, transparent cap and EndoringsTM) helped to improve the lateral and backward view of the mucosal folds(60-61,66-68,154,169,201).

These advancements demonstrated an improvement in the quality and performance of the procedure. However, none of the studies explored the impact on CE of the technologies. We aimed to assess the performance of a new marker of CE. We propose SP6 (Number of significant polyps detected per six minutes withdrawal time during colonoscopy) as the novel efficiency marker.

6.2 Methods

6.2.1 Study population

Patients who were scheduled for a screening or surveillance colonoscopy, between October 2014 and September 2016 at St Mark's Hospital were enrolled. Patients who had a previous surgical resection of the colon, inflammatory bowel disease and polyposis syndromes were excluded from the study. The study was conducted as a quality evaluation of missed colorectal polyps in BCSP. This study was reviewed and approved by North west London Hospitals NHS Trust review board.

6.2.2 Colonoscopy procedure

Patients were prepared with either a combination of Senna and 2 sachets of magnesium citrate (Citramag, Sanochemia) or polyethylene glycol preparations (Klean prep, Moviprep). A standard consent form for undergoing screening or surveillance colonoscopy was signed by all

patients as part of good clinical and standard practice Colonoscopies were performed with patients un sedated or under conscious sedation using midazolam and fentanyl. Patients were given 10-20mg of hyoscine N- butylbromide at the discretion of endoscopists. All procedures were performed by one of seven BCSP accredited colonoscopists, each having completed at least 5000 previous colonoscopies with caecal intubation rate of >95% and adenoma detection rate of >45%. The procedures were performed using Olympus 260 series colonoscopes (Lucera, Olympus, Tokyo, Japan). Patient demographics, procedural and performance variables of colonoscopies were retrospectively retrieved from the screening database. Histology of polyps were later retrieved from a clinical results database.

6.2.3 Definition and calculation of SP6

We performed a retrospective evaluation of prospectively collected data from our endoscopy database to assess the value of SP6 to compare different detection interventions EAC and SC. SP6 was calculated using the following simple formula.

$$SP6 = \frac{\text{Number of adenomas and sessile serrated polyps}}{\text{Total withdrawal time}} \times 6$$

Procedures which demand an additional session or advanced therapeutic modality such as endoscopic submucosal dissection, full thickness resection or laparoscopy assisted colonic resection were excluded from the analysis. These therapeutic procedures demand expert endoscopists and dedicated operating time.

6.2.4 Primary and secondary outcomes

Primary outcome of this study is to develop an efficiency marker incorporating adenomas and SSA/Ps. secondary outcome is to apply the efficiency formula to compare the performance of EAC and SC.

6.2.5 Statistical analysis

Continuous variables were compared using Mann-Whitney test. Un paired t test was used to compare the other variables. Fisher's exact test was used to analyse categorical variables. Analysis was done using Stata statistical programme (version 9.2)

6.3 Results

A total of 494 patients (age range 60-75 years) underwent surveillance colonoscopy during this period. Colonoscopy was performed for the following indications: screening following a positive FOBT (54%) and surveillance following previous polypectomy (46%). Table 26 summarises the procedural and polyp characteristics. There were no significant differences in the caecal intubation rate ($p=0.99$), caecal intubation time ($p=0.39$) or withdrawal time (WT) ($p=0.72$) between EAC and SC. However, total number of polyps and adenomas detected and resected were significantly higher in EAC than SC ($p=0.005$, and $p=0.0001$ respectively). Table 28 highlights the fact that there were no significant differences in WT between EAC and SC, when no polyps were detected during the procedure.

Table 26. Polyp and procedural characteristics

	EAC	SC	P value
Number of patients	256	238	0.86
Caecal intubation rate	99.6%	98.9%	0.96
Caecal intubation time (mean $\pm$ SD)	5.9 $\pm$ 3.0	7.1 $\pm$ 3.85	0.39
Withdrawal time (mean $\pm$ SD)	12.9 $\pm$ 4.5	11.8 $\pm$ 5.33	0.72
Number of polyps	343	159	0.001
Number of adenomas	285	112	0.0005
Number of SSA/Ps	28	20	1.0
ADR	84.4%	58.4%	0.004
SP6 (adenomas/SSA/P)	1.18	0.62	0.0004
MPP*	1.34	0.66	0.001

* MPP -Mean number of Polyps detected per Patient

Table 27. Correlation of WT when no polyps were detected during colonoscopy

	EAC	SC	P value
No of patients	27	61	<0.01
Withdrawal time (mean $\pm$ SD)	8.596 $\pm$ 2.28	6.24 $\pm$ 2.89	0.089

6.4 Discussion

There are several quality indicators in use to assess the quality of colonoscopic examinations including caecal intubation rate, WT more than 6 minutes and ADR(5,162,202-204). ADR has been extensively studied and considered as the most important performance marker of colonoscopy(11,170,205). It exhibits many advantages as a quality indicator. It is easy to calculate, understand and apply in clinical practice and in trials(206). Moreover large studies have shown that ADR correlates well with interval colorectal cancer (CRC) rate and mortality(11,170). However, there are fundamental problems with using ADR alone as a marker of colonoscopic quality and performance. Firstly, the ADR does not take into account detection of sessile serrated adenomas/polyps (SSA/P), thought to be the precursor lesions of 15-20% of all colorectal cancers(207). Secondly it has the potential for the colonoscopists to “switch off” after one adenoma has been detected (*“one and done phenomenon”*) and does not reward the detection of multiple polyps in the same patient(208). Thirdly, it does not measure how time-efficiently the endoscopist detects and removes polyps. This final point is of importance given the increasing volume of colonoscopy and the need to conduct colonoscopy lists in a timely and effective manner. Therefore, ADR cannot be used to assess the efficiency of an endoscopist, technique or colonoscopy aid.

We suggest a new and simple metric, SP6 (number of significant polyps detected per six minutes of withdrawal time at colonoscopy) as a quality and efficiency marker. SP6 considers detection and removal of all potential pre-cancerous lesions (adenomas and SSA/P) and

measures how efficiently those polyps are detected and removed. SP6 is easy to calculate, user friendly and a highly reproducible marker.

$$SP6 = \frac{\text{Number of adenomas and SSA/P}}{\text{Total withdrawal time}} \times 6$$

Total withdrawal time

In this study we have demonstrated that SP6 could be used to compare the performance of novel interventions or techniques. For example, our data showed that EAC significantly improve colonoscopy performance and overall efficiency of the procedure when compared to SC.

We have to bear in mind, when we interpret the performance of any novel devices or interventions, the quality of the procedure should not be compromised in order to improve the efficiency. Both quality and efficiency of the procedure should be enhanced in parallel. ESGE and ASGE mandated minimum withdrawal time of 6 minutes for diagnostic examinations. It is clearly mentioned in the guidelines that this figure only applies to examinations in which no polyps are found as detection and resection of polyps increases duration of the procedure(171,209). Table 27 shows that when no polypectomies were performed EAC (intervention) did not compromise the recommended withdrawal time of 6 minutes which highlights that the add on device does not compromise the quality when improving the overall efficiency of the procedure.

Finally, the quality indicators such as WT and ADR could be gamed, where the target measure is achieved but without reflecting the high-quality examination(208). The chances of potential gaming for SP6 is minimal as it incorporates time as an important assessment factor.

Conversely SP6 could be gamed during the procedure. This could occur when an endoscopist attempt to remove larger polyps (>2cm) and be tempted to complete the procedure within given time slot. This would result in incomplete polypectomy and recurrence. To minimise this effect,

we did not include procedures where large (> 2cm) polypectomies were performed. One could argue that when polyps of difficult nature (i.e. peri appendiceal location, recurrent/fibrotic polyps, polyps located within a diverticular segment) could take longer time or highly advanced therapeutic modality to resect and they could adversely affect SP6. During these difficult situations SP6 could be falsely low. However, this could be a positive argument for SP6 as it would clearly identify whether adjunct devices or interventions are superior in dealing with difficult polyps. In other words, SP6 marker could be used to compare the superiority of a device/intervention against each other.

In our cohort, we did not include any of the procedures which demands an additional session or advanced therapeutic modality such as endoscopic submucosal dissection, full thickness resection or laparoscopy assisted colonic resection as it may affect the SP6. Finally, SP 6 is a modifiable marker, if the recommended WT is changed in the future. For example, ESGE promotes an optimal WT of 10 minutes and the marker could evolve as SP10.

When we applied this formula to compare the two devices used in the DETECT study. The calculated SP6 for EAC and CAC would be 0.64 and 0.23, respectively. This means that when you perform EAC you would detect and treat 0.6 significant polyps per 6 minutes of withdrawal time and 0.2 polyps with CAC during the similar time period. This finding highlights that EAC is three times more efficient in detecting and treating polyps than CAC ($p < 0.001$). This example illustrates the utilization of SP6 to compare the efficiency of two devices.

In summary, our proposed efficiency marker SP6 may act as a meaningful new metric to demonstrate high quality and efficient examinations. SP6 could be used to compare the efficiency of endoscopists performance and novel endoscopic interventions or devices to aid the procedure. This new metric needs to be validated in randomised controlled trials prior to the implementation. It appears to be promising and perhaps more relevant and applicable to general clinical practice.

Chapter 7

Characterisation of colorectal polyps using Blue LASER Imaging (BLI): a narrow band imaging polyp classification system is equally applicable when using BLI

7.1 Background and aims

New technology in endoscopic imaging has revolutionised in-vivo characterisation of polyps enabling histology prediction in real time(106,210). Multiple clinical trials and a recent meta analysis of all available electronic chromoendoscopy techniques (NBI,I-Scan, FICE and BLI) have showed promising results to differentiate adenomatous polyps from non-adenomatous lesions(89,110-111,211-212) .

Endoscopic characterisation of polyps by virtual chromoendoscopy is mainly based on the visual appearance of vascular structures and surface pit patterns e.g. NBI(110).

Clinical application of narrow band imaging (NBI) has been validated and incorporated into routine endoscopy practice for more than 10 years. The Narrow band Imaging International Colorectal Endoscopic classification (NICE) is simple, user friendly and easy to learn (110). NBI technology uses a physical filter to exploit the capacity of haemoglobin to selectively absorb blue light (213-214). A new endoscope system “LASEREO,” which was developed by Fujifilm, uses a semiconductor LASER as a light source. It has a narrow-band light observation function without a customised optical filter. The LASEREO system uses two lasers with different wavelengths (119). BLI light is made from the combination of a strong LASER light with a wavelength of 410 nm, a weak LASER light with a wavelength of 450 nm, and

fluorescent light. The BLI mode is used as a high contrast signal to obtain information about vascular and surface pattern. By changing the intensity ratio of the two types of lasers, three observational modes can be selected through a combination of image processing with illumination suitable for white light and narrow band observation; White light Image(WLI), BLI bright (BLI- BR) and BLI. The BLI mode has an optical zoom magnification function up to 135 times(215).

Recently, Bisschops and colleagues described a new BASIC (BLI Adenoma Serrated International Classification) algorithm to characterise colonic polyps using BLI technology(216). Even though this classification showed particularly good inter observer agreement between experts, it has not been validated or used to assess the accuracy of predicting in-vivo histology. The BASIC classification may not be easy to apply in clinical practice due to model complexity. As NBI and BLI give similar visual appearances it may be possible to use the NICE classification when making optical diagnosis using for BLI.

The aim of this study was to validate NICE classification for BLI technology to differentiate neoplastic from non-neoplastic polyps less than 10mm in size.

7.2 Methods

Polyp images were collected prospectively by an experienced endoscopist who was not involved in the assessment phase of the study (R.R) between January and August 2015 as part of a clinical evaluation study. All procedures were performed with a Fujinon LASEREO colonoscope (Fujifilm, Tokyo, Japan) with BLI technology. Once a polyp was detected, it was washed to remove mucous and faecal residue, examined, and recorded using WL, BLI and BLI Bright, each image with and without magnification. Polyp size, location and morphology using Paris classification were documented. All polyps were biopsied or resected and sent for

histopathology which was used as the reference standard for subsequent analysis. Five experienced GI pathologist classified the specimens according to WHO guidelines (217).

Polyps of 10mm or more in size were not included in the study. As the NICE classification is not validated to differentiate HP from SSA/Ps, they were considered as one entity. A Research fellow not involved in image evaluation randomly selected still images of 25 polyps smaller than 10mm with known histology and the 6 different evaluation modes (WLI, WLI + mag, BLI, BLI + mag, BLI BRI, BLI BRI + mag (150 images in total). These images were incorporated into a slide show (one polyp image per slide). Subsequently, these images were arranged at random using a computer-generated sequence prior to expert review.

7.2.1 Endoscopist reading

The images were evaluated by four experienced Gastroenterologists with an interest in advanced electronic imaging. Although all reviewers possessed substantial experience in NBI, they had limited experience in BLI technology. Each reviewer had a formal teaching session (1 hour) on optical diagnosis looking at a series of separate polyp images using the BLI imaging modalities but applying the NICE classification. Following this they, reviewed the computer-generated data set of polyp images and applied the NICE classification to predict the optical diagnosis of images.

7.2.2 Evaluation of images

Reviewers were blinded to the polyp location and histopathological diagnosis. All 150 images were shown at a single session (figures 21-23). Each reviewer documented each 3 criteria of NICE classification as present/absent and expressed overall confidence of making an optical diagnosis and likely NICE category. Polyps were predicted to be NICE type 1/2/3 with high confidence if they had more than two out of three features of NICE classification. When there was uncertainty then the optical diagnosis was made with low confidence.



WL and WL Mag

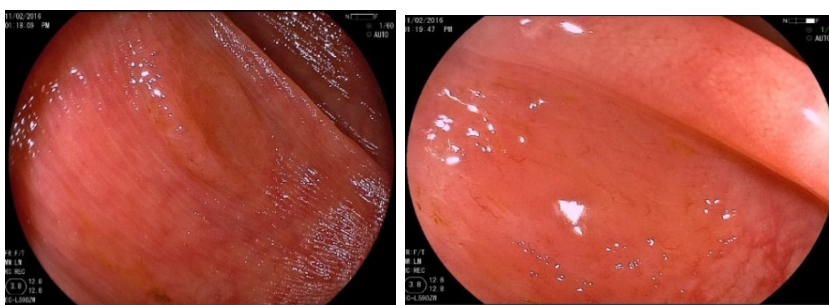


BLI BR and BLI BR mag

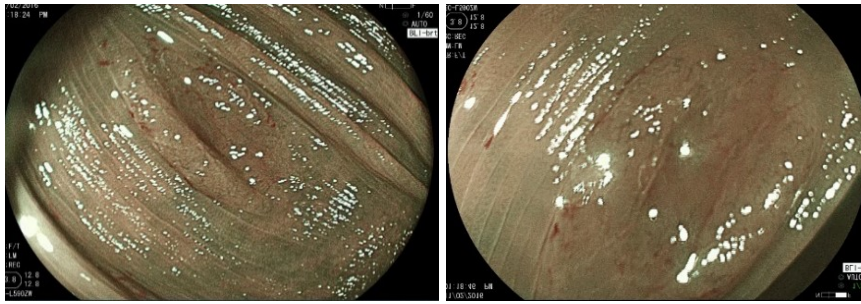


BLI and BLI Mag

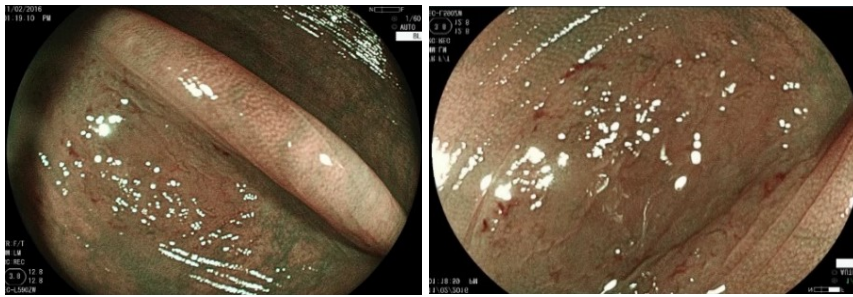
Figure 21. Hyperplastic polyp (NICE type 1)



WL and WL Mag



BLI BR and BLI BR mag



BLI and BLI Mag

Figure 22. Hyperplastic/Sessile serrated polyp (NICE type 1)

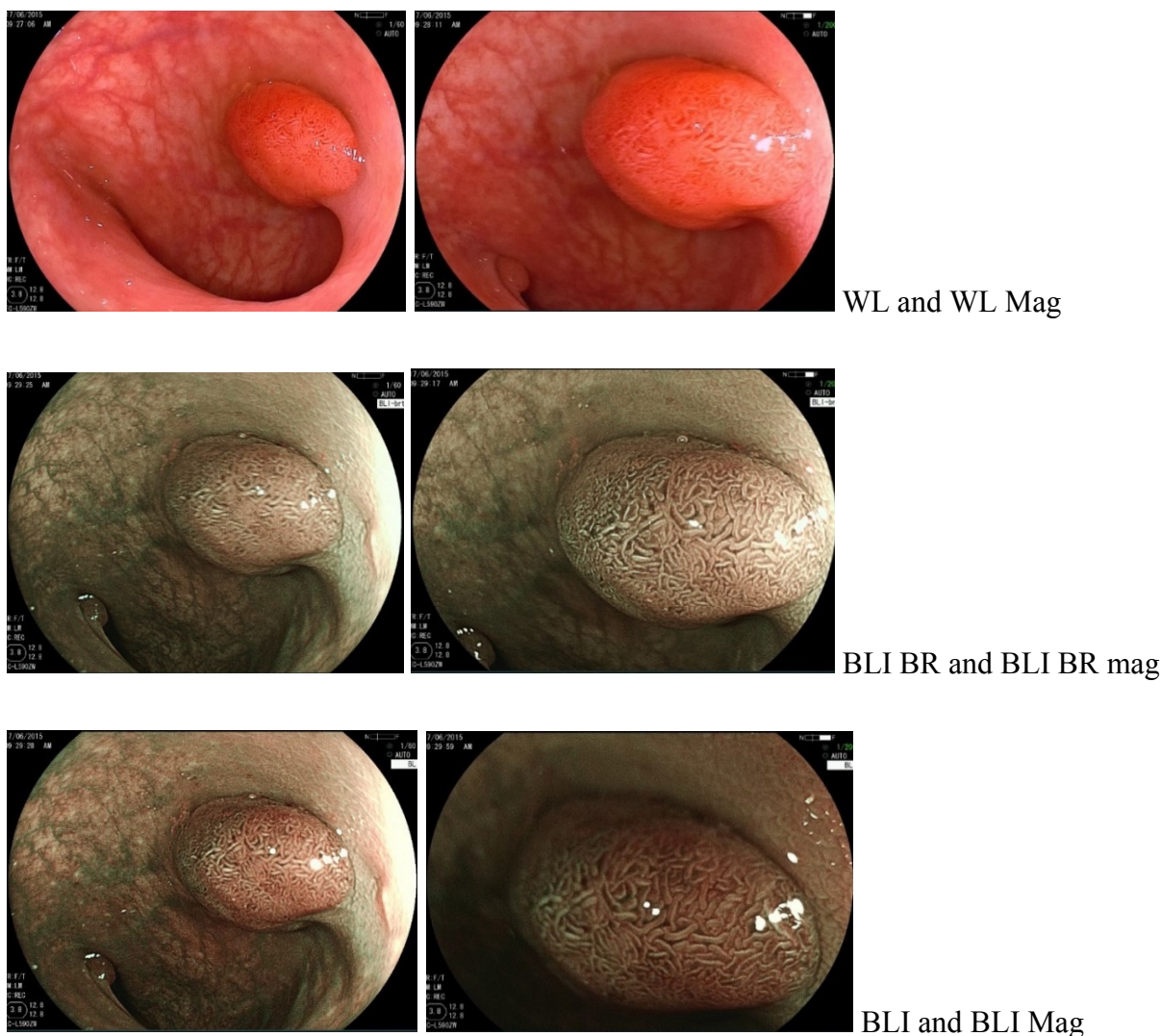


Figure 23. Adenoma (NICE type 2)

7.3 Statistical analysis

As this was a pilot evaluation study no power calculation was undertaken. The diagnostic value of at least two characteristics of the NICE classification were assessed. The analysis of sensitivity was restricted to true positive cases (i.e. adenomas) and the analysis of specificity was limited to true negative cases (i.e. HP and SSA/Ps). Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated using 95% confidence intervals. Robust standard errors were used to take into account the non-independence of the data as each polyp was included in the analysis 4 times(218-219). Fisher's

exact test was used to compare the high and low confidence estimates. The agreement between reviewers were assessed using kappa statistic. Data were reported according to STARD and QUADAS guidelines(220-221).

7.3.1 Primary outcome

Primary outcomes were to assess

1. diagnostic accuracy of NBI criteria when applied to BLI, images
2. diagnostic accuracy according to confidence levels.

7.3.2 Secondary outcomes

Secondary outcomes were diagnostic accuracy of BLI for differentiating between adenomatous and no adenomatous polyp histology types and to assess inter-observer agreement between each expert reviewer.

7.4 Results

7.4.1 Polyp characteristics

A total of 25 polyps from 20 patients were included in the analysis. WLI, BLI, BLI -BR, BLI mag, and BLI-BR mag images were reviewed. 64% of them were adenomas, 32% were a combination of HP and SSA/Ps, while one polyp contained cancer within it (4%). Mean polyp size was 4.7mm (SD: 2.4mm). Location of polyps were caecum (12%). Ascending, transverse, descending colon and rectum 16% each, sigmoid 24%. 45% of polyps were diminutive (<5mm) and median polyp size of 5.2mm (range 3-9mm).

7.4.2 Accuracy and inter observer agreement

Accuracy of BLI technology was calculated as a proportion of true positive and true negative in all evaluated images. When not considering the level of confidence, the overall sensitivity,

specificity, and accuracy in diagnosing adenomas for BLI were 0.95(95% CI,0.88-0.98), 0.5(95% CI 0.12-0.88) and 0.92(95% CI 0.84-0.96). When magnification was applied the corresponding values were 0.96(95% CI 0.89-.0.99), 0.78(95% CI 0.69-0.87) and 0.93(95% CI 0.86-0.97). respectively. The similar values for BLI -BR and BLI -BR with magnification were 0.95(95% CI 0.89-0.99), 0.6(95% CI 0.15-0.95) and 0.94(95% CI 0.87-0.98 respectively. There were no improvements when magnification was applied to BLI -BR mode. (table 29). Expert reviewers had good overall agreement ($k=0.63$;95% CI 0.52-0.74).

Table 28. Performance of all three modalities

Mode	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
WLI	0.8(0.7,0.87)	0.5(0.68,0.93)	0.79(0.69,0.86)
WLI MAG	0.84(0.75,0.91)	0.6(0.15,0.95)	0.83(0.74,0.9)
BLI BRI	0.95(0.89,0.99)	0.6(0.15,0.95)	0.94(0.87,0.98)
BLI BRI MAG	0.95(0.89,0.99)	0.82(0.75,0.92)	0.94(0.87,0.98)
BLI	0.95(0.88,0.98)	0.5(0.12,0.88)	0.92(0.84,0.96)
BLI MAG	0.96(0.89,0.99)	0.78(0.69,0.87)	0.93(0.86,0.97)

When the magnified images were used reader confidence levels improved significantly for BLI and BLI-BR modes (Figure 24): BLI (54% and 92%, $p<0.0001$) and BLI-BR (55% and 93%, $p<0.0001$).

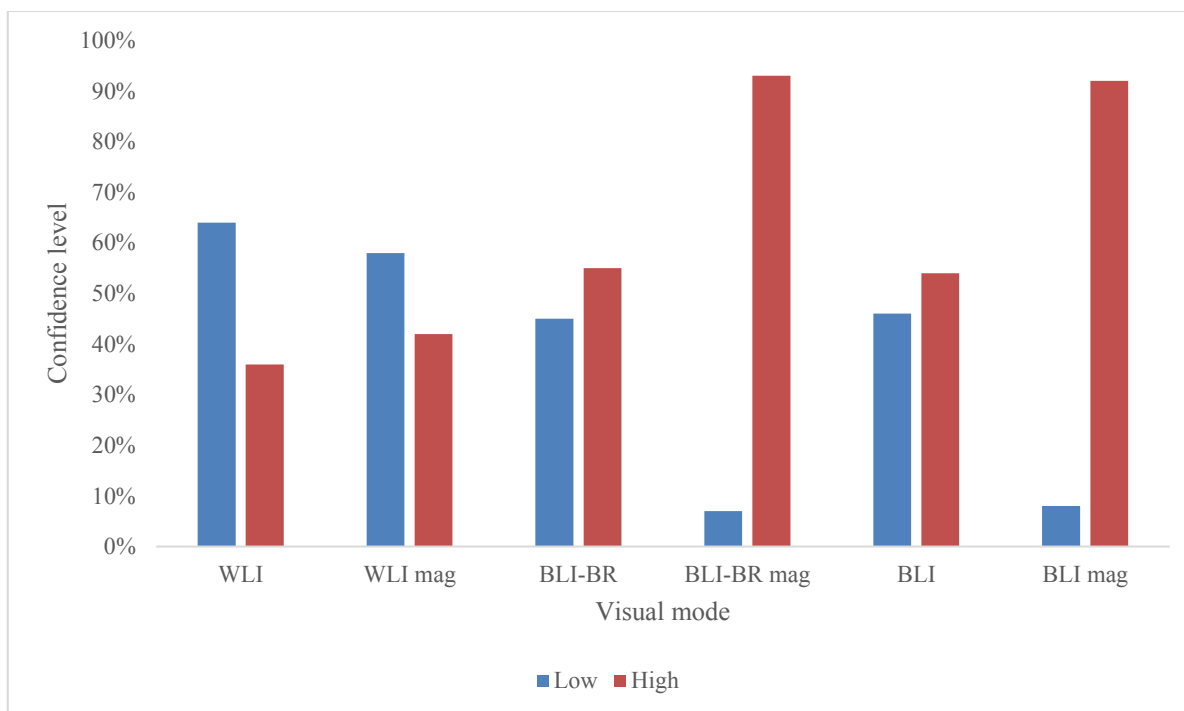


Figure 24. Reader confidence levels with non-magnified and magnified images

7.4.3 Reading accuracy as per NICE combination criteria

The diagnostic values of the criteria used in combination when applied to BLI images is displayed in table 2. Across all polyps and reviewers, sensitivity, specificity, accuracy, PPV and NPV for colour and surface pattern were 80%,100%,89%,100% and 81% respectively. When magnification was applied the parameters changed a little.

Remarkably similar trends were noted for the BLI BR modality across any combination of NICE criteria (table 30 & 31).

Table 29. Performance characteristics of NBI criteria when used in isolation and combination for BLI BRI mode (with and without magnification)

Criteria	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
BLI BRI					
Combination of 2 criteria					
Colour and surface	0.85(0.61,0.96)	0.83(0.36,0.99)	0.85(0.66,0.94)	0.94(0.71,0.99)	0.62(0.26,0.9)
Colour and Vessels	0.84(0.54,0.97)	0.86(0.42,0.99)	0.85(0.63,0.96)	0.92(0.6,0.99)	0.75(0.35,0.95)
All 3 criteria					
Colour, vessels and surface	1(0.86,1)	0.9(0.68,0.98)	0.96(0.86,0.99)	0.93(0.78,0.99)	1(0.79,1)
BLI BRI MAG					
Combination of 2 criteria					
Colour and surface	0.5(0.09,0.91)	1(0.31,1)	0.71(0.35,0.92)	1(0.2,1)	0.6(0.17,0.93)
Colour and Vessels	0.5(0.09,0.91)	1(0.19,1)	0.67(0.23,0.96)	1(0.2,1)	0.5(0.28,0.73)
All 3 criteria					
Colour, vessels and surface	0.96(0.88,0.99)	0.96(0.76,1)	0.96(0.89,0.99)	0.98(0.9,1)	0.92(0.72,0.99)

Table 30. Performance characteristics of NBI criteria when used in isolation and combination for BLI mode (with and without magnification)

Criteria	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
BLI					
Combination of 2 criteria					
Colour and surface	0.8(0.51,0.95)	1(0.72,1)	0.89(0.72,0.97)	1(0.7,1)	0.81(0.54,0.95)
Colour and Vessels	0.83(0.58,0.96)	0.75(0.22,0.99)	0.82(0.61,0.93)	0.94(0.68,1)	0.5(0.14,0.86)
All 3 criteria					
Colour, vessels and surface	0.94(0.79,0.99)	0.94(0.68,1)	0.94(0.83,0.99)	0.97(0.82,1)	0.88(0.62,0.98)
BLI MAG					
Combination of 2 criteria					
Colour and surface	0.66(0.12,0.98)	0.75(0.22,0.99)	0.28(0.35,0.92)	0.67(0.12,0.98)	0.33(0.02,0.87)
Colour and Vessels	0(0,0.94)	1(0.05,1.06)	0	NA	NA
All 3 criteria					
Colour, vessels, and surface	0.96(0.88,0.99)	0.96(0.76,1)	0.96(0.89,0.99)	0.98(0.9,1)	0.92(0.72,0.99)

7.5 Discussion

The results of our study strongly support the application of the NICE classification to BLI technology (both BLI modes) evidenced by acceptably high accuracy and interobserver agreement.

BLI BR mode is generated by an appropriate combination of WL and BLI and helps to assess the surface structures and in particular vessel pattern on the polyp surface(121).

When the performance of the NICE classification was assessed, we did not consider any single criteria in isolation, rather we examined two or more criteria to predict polyp histology. The main reason for this approach was that in the original NICE classification (110) validation study, when a single criterion (colour or vessels or surface pattern) was applied, gastroenterology fellows attained accuracy and sensitivity and negative predictive value less than 90%, which is below the PIVI standards recommended by ASGE(134). However, when all three criteria were combined, they attained accuracy of 92% and NPV of 93%. Our study mirrored remarkably similar findings; when all 3 NICE criteria were applied, accuracy and NPV reached 96% and 92% respectively.

In the current study a high confidence diagnosis was made in 79% of cases, which is similar to the 80% reported in the NICE validation study(110) These findings correlated with high accuracy levels (94-96%) when the NICE classification was applied to BLI images.

Bisschops et al. recently published the BASIC classification for polyp characterisation using BLI technology. In that study, optical magnification improved interobserver agreement for most of the descriptors (pit pattern from 0.69 to 0.77, $p=0.02$ and vascular pattern from 0.81 to 0.85, $p=0.02$). The main reason for improvement was due to the increased visualisation of both pit and vascular pattern with high confidence(216). We observed similar findings in our study. Confidence levels were significantly increased for both BLI modes when optical magnification was applied; BLI (55.3% to 91.2%, $p<0.0001$) and BLI BR (55.4% to 91.3%, $p<0.0001$).

Unlike the NICE classification, the BASIC classification(216) incorporated features of NICE and the WASP classification for differentiating hyperplastic from sessile serrated polyps (110,138) . Although BASIC therefore may be considered a more comprehensive classification system than NICE the key aspect of a “DISCARD” strategy is to make high confidence optical diagnosis on small adenomas and avoid sending these polyps for histopathology. NICE is

widely used and recognised and applicable to magnified and non-magnified images, therefore easily incorporated into routine practice, particularly where clinicians are using both NBI and BLI systems during colonoscopy practice.

Recently Repici and colleagues explored the application of the NICE classification to the FICE system(214). They created a video library of 55 small polyps (<1cm), captured with the FICE system and these were assessed by six experienced endoscopists. Across all the readers the accuracy, NPV and area under the curve were 77%,75% and 0.82, respectively. Interobserver agreement with the NICE was only moderate ($k=0.51$). One of the reasons for poor reproducibility of NICE classification for FICE technology may have been that FICE is a first-generation post image processing technology with less clarity and definition than current NBI and BLI systems.

The strengths of the current study are that it included four expert endoscopists and a variety of neoplastic and nonneoplastic polyps simulating routine clinical practice. Limitations of this include the fact that it was a single centre study and the images were retrospectively retrieved from an image gallery and still images were used rather than video recordings, therefore our study may not be entirely representative of clinical practice. Also, we could not assess the benchmark provided by ASGE for the optical diagnosis, resect and discard strategy, of assigning post polypectomy surveillance based on optical diagnosis.

This study appears to show that the NICE classification, a widely used and accepted tool for NBI is equally applicable to BLI technology for classification of small and diminutive polyps. However, before adopting NICE for polyp characterisation with the BLI technology the findings need to be validated in clinical trials, in particular looking at use of NICE with BLI to facilitate a “resect and discard policy” for diminutive adenomas.

Chapter 8

Prevalence and distribution of sessile serrated adenomas/polyps (SSA/P) in the colon

8.1 Background and aims

Recent studies showed that SSA/Ps are the likely precursor lesions for 15-30% of CRC cases and that the “serrated pathway” is significantly over-represented in interval or post-colonoscopy colorectal cancers (222-223), suggesting that SSA/P’s are either missed at colonoscopy and/or can rapidly transition to cancer . Histologically, SSA/Ps are characterised by a saw toothed appearance of the crypts (224) and endoscopically appear as subtle, often minimally-elevated lesions with surface mucus and reduced surface vascularity compared to adenomas(80). The true prevalence of SSA/Ps has been difficult to determine accurately due to inconsistent diagnostic endoscopic and histological criteria (225-226). However, recently the diagnostic criteria to differentiate HPs from SSA/Ps have been established. It is known that there are significant variations in polyp detection rates among different endoscopists who may use different image enhancing modalities for detection and have different criteria for performing colonoscopy (227). SSA/P’s are easily overlooked due to their subtle appearance. The most frequent sentinel sign suggestive of an SSA/P is the presence of an adherent mucous cap often producing a dome shaped protrusion of the polyp above the mucosa(228). Recently, a group of international experts evaluated 150 polyp images and identified the following features: cloud like surface, indistinct borders, irregular shape (figure 25) and the presence of dark spots inside crypts(80). Although SSP’s have cancer potential it appears that the other type of serrated polyp, the hyperplastic polyp, particularly when identified in the recto-sigmoid

area, is not associated with an increased cancer risk (229-230). WASP classification described the a system to differentiate HPs from SSA/Ps(138).The ASGE and ESGE recommend that if hyperplastic polyps are seen at the recto-sigmoid they can be left in-situ without resection provided adenomatous histology is excluded by optical diagnosis with >90% negative predictive value (134,139). However, a criticism of optical diagnosis is that it is hard to distinguish hyperplastic polyps and SSA/P's and potentially leaving SSA/Ps without resection may risk progression to CRC. Hence, it is important to define the true prevalence of SSA/Ps, particularly in the distal colon prior to the implementation of OD. The aim of this study is to determine the prevalence of SSA/Ps in rectum and distal sigmoid colon at screening colonoscopy and flexible sigmoidoscopy (bowel scope).

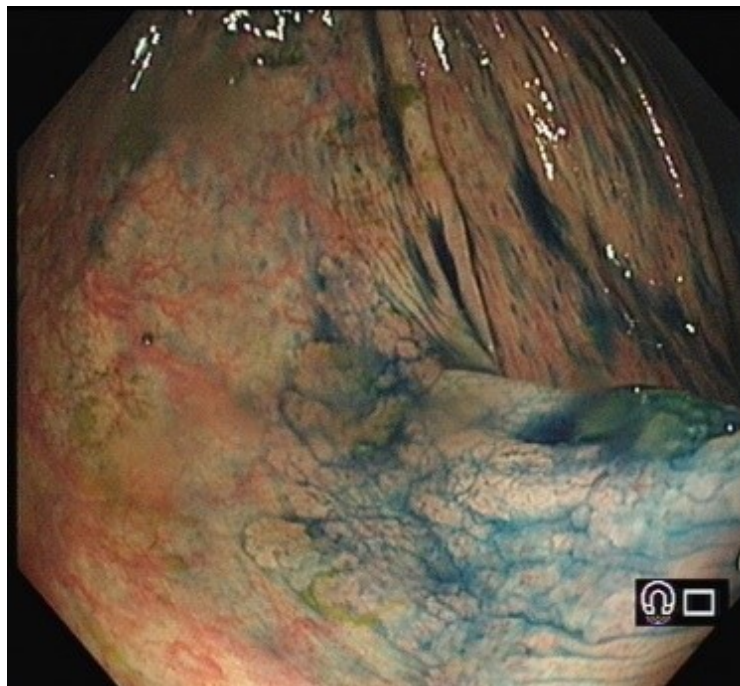


Figure 25. Sessile serrated polyp with indistinct margin and subtle mucosal abnormality.
Indigo carmine delineates the margins

8.2 Methods

This study was conducted as a cross sectional retrospective study from a prospectively collected bowel cancer screening data base. All screening colonoscopies and bowel scopes were performed by bowel cancer screening accredited endoscopists.

All data were retrieved by a research fellow and no additional interventions were carried out for this study. Hence, ethical approval of the study protocol by our institutional research and development board was not required. It was carried as a service development project and reviewed and registered by the trust (SUR.StM.15.006)

8.2.1 Patient selection

All patients who underwent a screening colonoscopy or bowel scope between August 2014 and April 2015 were included in the study. Incomplete procedures were excluded from the analysis.

8.2.2 Colonoscopy and bowel scope procedures and collection of data

8.2.2.1 *Colonoscopy procedure*

Patients were prepared with either a combination of Senna and 2 sachets of magnesium citrate (Citramag, Sanochemia, Bristol, UK) or polyethylene glycol-based solutions preparations (Klean prep, Moviprep). A standard consent form for undergoing colonoscopy was signed by all patients as part of good clinical and standard practice. Colonoscopies were performed with patients unsedated or under conscious sedation using midazolam and fentanyl. Patients were given 10-20mg of hyoscine N- butylbromide at the discretion of endoscopists. Procedures were performed by experienced (more than 5000 screening procedures) cancer screening accredited colonoscopists.

8.2.2.2 *Flexible sigmoidoscopy procedure*

Participants had a phosphate enema two hours prior to the procedure. Patients with poor bowel preparation (semi solid stools could not be suctioned or flushed away with water) were given

a 2nd phosphate enema through the scope channel and the procedure was repeated. Patients with poor bowel preparation despite two enemas were excluded. Procedures were performed either with Entonox or without any medications. None of the patients were given conscious sedation or propofol. All procedures were performed by bowel cancer screening accredited GI fellows in training or nurse endoscopists (Bowel scope accredited).

All procedures were performed with high definition Olympus Lucera CFC 260 or 290 series colonoscopes. Procedural data were obtained from endoscopy reporting system (Endosoft, USA). We collected patient demographics and histology findings from clinical notes and pathology reports. All polyps were resected and sent for histopathology examination.

8.2.3 Histopathological evaluation

Resected polyps were evaluated by experienced gastrointestinal pathologists through haematoxylin and eosin (H&E) staining. Moreover, all SSA/Ps were reviewed by two different gastrointestinal histopathologists. With respect to serrated lesions, HPs were diagnosed if polyps showed a luminal portion with a “saw tooth” appearance, elongated and straight crypts, narrow and hyperchromatic at the base, small and regular nuclei with a round shape and basally located in the luminal half of the crypt (figure 26). SSAs/Ps were diagnosed when there were architectural disturbances of the bases of the crypts (such as marked dilation of crypts with flattened, horizontal bases; “L, inverted T, hockey stick or boot” shaped crypt bases; moderate dilation without flattening, at least three adjacent abnormal crypts and serration variably present throughout gland length(231).

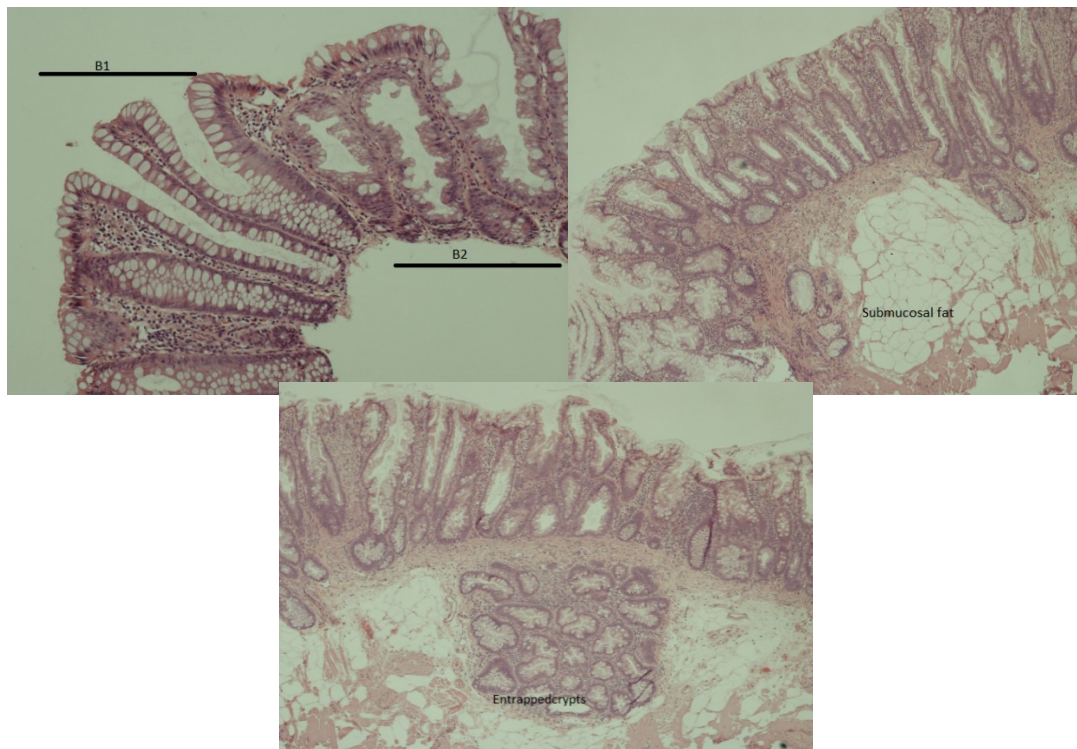


Figure 26. Histological features of sessile serrated polyp. B1 & B2 – complete resection of serrated polyp showing serration with a rim of normal colonic mucosa. Serrated appearance at the base of the crypts, horizontalization of the crypts, Submucosal fat and entrapped crypts in submucosal layer found in a proportion of serrated polyps.

8.2.4 Primary and secondary outcomes

The primary outcomes of this study were the prevalence and distribution of sub types of serrated polyps. The secondary outcome was to describe the distribution and characteristics of serrated polyps in the recto-sigmoid area.

8.2.5 Statistical analysis

The prevalence was described as the proportion of procedures with a positive pathology(polyps) divided by the total number of procedures (colonoscopy/flexible sigmoidoscopy) and presented as a percentage. Mean size and standard deviation (SD) of the

detected colonic polyps were also calculated. SPSS version 21 was used for statistical analysis (SPSS, IBM, Armonk, USA).

8.3 Results

8.3.1 Colonoscopies and detected polyps

During the study period, 500 patients had a screening colonoscopy. The mean age was 66.3 ± 6.1 years and 59% were males. 99.6% of colonoscopies (498/500) were completed to caecum or terminal ileum. The remaining two colonoscopies were incomplete due to sub optimal or poor bowel preparation and a CT virtual colonoscopy was organised to assess the proximal colon. In total, 1006 polyps were detected. Their mean size was 6 ± 7.2 mm. Of these polyps, 679 (67.5%) were adenomas (tubular and tubular villous), 121 (12%) were HPs and 43 (4.3%) were SSA/Ps (Table 32). None of the SSAs/Ps had associated dysplasia. The remaining detected lesions (16.8%) were represented by: inflammatory polyps, normal colon mucosa, adenocarcinoma, juvenile polyps, lymphoid aggregates, vascular malformations, and gastrointestinal stromal tumours (GIST).

8.3.2 Bowel scope and detected polyps

97.6% of FS (488/500) were completed to the proximal sigmoid colon. The remaining twelve procedures were incomplete due to discomfort or poor bowel preparation. Bowel scope detected a total number of 249 polyps. Their mean size was 3.4 ± 3.9 mm. Of these polyps, 79 (32%) were adenomas (tubular and tubular villous), 71 (28.5%) were HPs and 6 (2.4%) were SSAs/Ps. Only one of the detected SSA/Ps had associated dysplasia (low grade). The remaining detected lesions (37.1%) were represented by: inflammatory polyps, normal colon mucosa, neuroendocrine tumour (NET), lymphoma and leiomyoma (Table 31).

Table 31. Polyp characteristics

Number of patients	Colonoscopy	FS
--------------------	-------------	----

	N=498	N=488
Total number of polyps	1006	249
Mean polyp size (mm $\pm$ SD)	6 $\pm$ 7.2	3.4 $\pm$ 3.9
Adenomas	679	79
Hyperplastic polyps	121	71
Others	206	99
Sessile serrated polyps	43	06
Prevalence of SSA/P	4.27%	2.4%

8.3.3 Prevalence of SSA/Ps by colonic segments

43 SSA/Ps were identified at screening colonoscopies (4.3% of all detected polyps) and only 6 at screening bowel scope procedures (2.4% of all detected polyps), which equates to an overall prevalence of 3.9% (49/1255 polyps). Table 32 summarises the SSA/Ps prevalence and other polyp data from our cohort. The highest prevalence of SSAs/Ps was found in the caecum (7.9% of all caecal polyps; size range 3-13 mm), followed by the ascending colon (5.4%, size range 4-15 mm), sigmoid colon (4.1%, size range 3-10 mm), rectum (3.9%, size range 2-9 mm), transverse colon (3.2%, size range 4-10 mm), hepatic flexure (2.7%, size 50 mm) and descending colon (1.5%, size range 2-6 mm). Table 33 summarizes the prevalence of SSAs/Ps in each colonic segment.

Table 32. Polyps location in colorectum (both screening colonoscopies and bowel scope procedures)

Site	Polyps colon	Polyps FS	Total number of polyps	SSA/Ps colon	SSA/Ps FS	Total number of SSA/Ps	Prevalence
Rectum	127	95	222	07	01	08	3.9%
Sigmoid	201	119	320	08	05	13	4.1%
Descending colon	103	30	133	02	00	02	1.5%
Transverse colon	217	NA	217	07	NA	07	3.2%

Ascending colon	168	NA	168	09	NA	09	5.4%
Caecum	114	NA	114	09	NA	09	7.9%
Splenic flexure	37	NA	37	00	NA	00	00
Hepatic flexure	37	NA	37	01	NA	01	2.7%

Table 33. Proportion and size of SSA/P in different site of colon for both screening procedures

Location	Prevalence	Median size (mm)
Rectum	3.9%	3
Sigmoid colon	4.1%	5
Descending colon	1.5%	2
Splenic flexure	0%	0
Transverse colon	3.2%	6
Hepatic flexure	2.7%	40
Ascending colon	5.4%	6
Caecum	7.9%	6

8.3.4 Proportions and characteristics of SSA/Ps in recto-sigmoid colon

In total, screening colonoscopies and bowel scopes detected 21 SSA/Ps in the recto-sigmoid colon, which equals to a 3.9% of all recto-sigmoid polyps (table 35). The size of all SSA/Ps found in the recto-sigmoid area ranged between 2 mm and 10 mm and Paris classification was as follow: Is 94% and IIa 6%. Only one (4.8%) serrated lesion showed dysplasia (low grade) at histopathological examination.

With respect to HPs and adenomas (both tubular and tubular villous), the prevalence in the recto-sigmoid area was 22.5% and 46.8%, respectively. Prevalence and median size of SSA/Ps were described in table 34.

Considering the colonoscopy group of patients alone, 43 SSA/Ps were detected and removed. These 43 serrated lesions were found in a total of 26 patients. Of these patients, only 4 (15.4%) had serrated lesions in the recto-sigmoid area with coexisting polyps in the proximal colon. In particular, the polyps found in the proximal colon were represented by adenomas (both tubular and tubular villous, all with low grade dysplasia) and other sessile serrated lesions (table 35). Table 36 illustrates the different histological types of polyps in recto sigmoid area.

Table 34. Proportions and characteristics of SSA/P in recto sigmoid segment during colonoscopy alone

	Number	Percentage
Number of SSA/P in recto sigmoid	15/328	4.6%
Number of SSA/P with dysplasia	0	0
Number of patients with synchronous adenoma/SSA/P (>5mm) in proximal colon	4/15	26%

Table 35. Polyps detected during bowel scope screening procedures alone

	Rectum	Sigmoid colon
Hyperplastic polyps	56%	41%
Adenomas	17%	43%
SSA/P	1%	5%
Others	21%	29%

8.4 Discussion

Most hyperplastic polyps especially in the recto-sigmoid area , appear to have an indolent course and should be distinguished from pre malignant SSA/Ps(232). The prevalence of SSA/Ps varies widely in the published literature. The following reasons could explain this finding. Firstly, SSA/Ps can be difficult to detect endoscopically, even by experts, as they are often covered with transparent mucous and have undefined borders(228). Secondly, the histopathological differentiation of SSA/Ps from HPs is also difficult even in the hands of expert histopathologists(225-226). Knowledge about the prevalence, size and location of SSA/Ps is of value to ensure high quality examinations and to allocate appropriate surveillance intervals as surveillance recommendations now take into account the presence of both adenomas and SSA/Ps (233). Additionally, improved detection of SSA/P's indicates a high-

quality examination (234) and the presence of SSA/P's has been shown to be associated with synchronous advanced neoplasia (142).

In this retrospective study we demonstrated that the prevalence of SSA/Ps is relatively low (2.8%) in diminutive polyps (<5mm) in recto-sigmoid area while the overall prevalence was 3.9% in the distal colon. Our Findings were compatible with the published prevalence of recto-sigmoid SSA/Ps. In a recent study, the incidence of diminutive rectosigmoid SSA/Ps was between 0.6-2.1% as interpreted by three expert GI pathologist, who examined 513 'hyperplastic looking polyp' specimens resected by an expert endoscopist (140). In another study, 25 endoscopists performed 3743 colonoscopies and resected 4251 polyps including 974 HPs (22.9%) and 399 SSA/Ps (9.4%). The prevalence of SSA/Ps less than 10mm in recto sigmoid area was 3.3%(142).

Endoscopic discrimination of HPs from SSA/Ps is challenging and depends on the level of experience of endoscopists(184). The NICE classification is not helpful in differentiating these two sub types as both show NICE type 1 features(110). Recently, WASP criteria and the BASIC classification have been validated for endoscopic differentiation of SSA/Ps from HPs using following discriminatory features of SSA/Ps (138,216).

Our data highlight the fact that a small, (3.9% overall and 2.8% of polyps <5mm) but significant proportion of SSA/Ps tend to cluster in recto-sigmoid area. Therefore, the practicing colonoscopists cannot simply dismiss all serrated-appearing polyps in the recto-sigmoid as being hyperplastic. Prior to the implementation of optical diagnosis in routine clinical practice, it would be reassuring to be able to differentiate HPs from SSA/Ps and use of magnification for diminutive polyps may be helpful (140) as well as utilising the WASP and BASIC classifications. Furthermore, our study accentuated the importance of careful scrutinization of diminutive and small 'hyperplastic looking polyps' for the possibility of SSA/P's using advanced imaging technology such as NBI, BLI or i-scan preferably with magnification.

Strengths of this study were a large sample size and the analysis of both colonoscopy and flexible sigmoidoscopy procedures; therefore, the results are more generalisable to day to day clinical practice. Data was retrieved from prospectively collected data of a bowel cancer screening programme. Hence the quality assurance of all procedures is kept to a high standard. Limitations of this study are its retrospective nature and the observational design. Secondly, colonoscopies were performed by experienced endoscopists, who already practice a diagnose and disregard strategy for recto sigmoid hyperplastic looking polyps, therefore the true prevalence may be slightly different than mentioned in this study. To rectify this phenomenon, we carried out a separate analysis of bowel scope procedures as these procedures were performed by moderately experienced endoscopists (fellows in GI training and screening accredited nurse endoscopists) who are more likely to resect all visible polyps and not practice optical diagnosis.. Hence the prevalence from flexible sigmoidoscopy screening procedures could reflect a truer prevalence of serrated polyps in the rectum and sigmoid.

In summary, our data showed that the detection rate of serrated polyps in the recto-sigmoid area was low and comparable with previous reports. Only one serrated polyp (6mm in size) harboured dysplasia. We recommend a careful assessment of small polyps for advanced histology and to identify the small proportion of SSA/Ps in recto sigmoid colon using advanced imaging techniques and magnification. If we could perform a detailed and meticulous scrutinization of those polyps with high confidence, then ‘diagnose and disregard’ strategy of hyperplastic polyps (<5mm) in the recto sigmoid area is feasible. High quality images of the polyps should be kept in records for audit and quality assurance purposes.

Chapter 9

Learning curve for the optical diagnosis of colorectal polyps using cumulative sum analysis

9.1 Background and Aims

The number and size of neoplastic polyps (adenomas and SSA/Ps) detected at colonoscopy are one of the best determinants of long term risk of CRC and define the surveillance interval following a complete colonoscopy (4). Diminutive and small colorectal polyps(<9mm) have less malignant potential than larger (>10mm) polyps in the medium term. The possibility of harbouring advanced histological features or cancer in diminutive and small polyps are 0.2% and 0.8% respectively(235). Optical diagnosis for diminutive and small colorectal polyps is an attractive option to reduce histopathology costs and to streamline patient care (236). The American Society of Gastrointestinal Endoscopy (ASGE) in its PIVI statement recommended a >90% diagnostic threshold for real time endoscopic diagnosis of diminutive colorectal polyps. These thresholds were $\geq 90\%$ agreement between optical diagnosis based post polypectomy surveillance intervals and those defined by the gold standard histology, and a $\geq 90\%$ negative predictive value (NPV) for adenomas when the diagnosis were made with high confidence in the rectosigmoid colon (134). A recent meta-analysis which included 28 studies and a total of 6280 polyps with 63% neoplastic polyps, achieved ASGE thresholds for optical diagnosis with 93% concordance of surveillance interval and NPV for high confidence predictions between 90-96% (237). This systematic review focused on studies using Narrow Band Imaging (NBI) as the virtual chromoendoscopy technique. To adopt optical diagnosis in clinical practice, endoscopists must demonstrate competence in the process. The learning curve

to accurately assess the surface and pit pattern of polyps appears using NBI appears to be short and simple (238) however relatively few studies have explored the learning curve of optical diagnosis(OD) with NBI (239-240). In these studies, most of the participating endoscopists have been highly experienced with 1000's of previous polyp observations. The learning curve of OD for less experienced endoscopists still in training is yet to be determined.

The aim of this study therefore was to evaluate the minimum number of polyp observations needed to achieve and maintain optical diagnostic performance for gastrointestinal doctors in training.

9.2 Methods

9.2.1 Endoscopists and training

Four GI trainees participated in this observational pilot study. All of them were certified by the Joint Advisory Group for GI endoscopy (JAG) as fully certified colonoscopists with an annual colonoscopy volume between 300-800 procedures. They were all familiar with NBI technology and had some knowledge of NICE and WASP classifications for small polyps(138). Prior to the commencement of the study, they were given, a validated training module on OD based on NICE and WASP classification(110,138). During the study period between January 2016 to August 2016, each trainee documented the OD of polyps less than 10mm in size. All polyps were resected and sent for histopathology. Confidence levels (high or low) of OD were noted at the same time. Patient demographics and polyp details (site, size, and histology) were collected prospectively. OD of each polyp was compared against the polyp histology. Polyps without the histological confirmation were excluded from the analysis. Polyps with high confidence diagnostic prediction were included in the subsequent analysis. Every trainee had ongoing feedback on their performance by an experienced endoscopist who is an expert in NBI optical diagnosis.

9.2.2 Endoscopy procedures and feedback

During consecutive colonoscopy or flexible sigmoidoscopy, polyps <10mm were assessed by WL and NBI. Polyps site, size and morphology were described and documented. Using NICE and WASP classification, colonoscopists documented the OD and the diagnostic confidence levels as high or low. Polyps where histology was not available such as when the polyp was not retrieved post resection, were excluded from the analysis. Trainees were given feedback every 2 weeks on how well their optical diagnosis correlated with histology. If their performance was sub optimal, then they retook the training module and attended expert colonoscopist's lists for further training.

9.2.3 Histopathological evaluation

All resected polyps were sent for histopathological assessment. Histopathologists classified specimens according to WHO guidelines. All polyps <10mm were scrutinised as per the NICE and WASP classifications and histology was used as the reference standard for assessing the accuracy of OD.

9.2.4 Primary and secondary outcomes

The primary outcome was to evaluate the learning curve of OD to suggest the minimum number of polyp observations needed to achieve optical diagnostic threshold defined by PIVI standards (134). Secondary outcome measures were to assess each trainee's performance and the impact of any intervention needed to maintain performance standards.

9.2.5 Statistical analysis

Analysis of variance and Chi-square test were used for comparing baseline patient and pathology characteristics of groups classified by each trainee who performed colonoscopy/flexible sigmoidoscopy. Next, the diagnostic performance of trainees was assessed against the histology of resected polyps.

Cumulative sum (CUSUM) analysis was used to assess the learning curve of OD for each small polyp (<10mm). This is a method of continuously assessing the performance of an individual or process against the predetermined PIVI standards. In the CUSUM plot, each polyp observation was plotted in sequence along the x-axis. when a success occurred, a constant of S was subtracted from the CUSUM score. When a failure occurred, a constant of $1-S$ was added to the CUSUM score. Therefore, a positive trend in the CUSUM plot indicated failure, whereas a negative trend indicated success(241-243). A constant of S based on acceptable failure rate (P_0 , level of inherent error procedure calculated correctly) and unacceptable failure rate (P_1 , where $P_1 - P_0$ represents the maximum acceptable level of human error). In our study, P_0 value was defined as per PIVI standards. Next a P_1 value was set to twice the value of P_0 . Typical values for type 1 and type II errors (alpha and beta respectively) are 10%, and unlike power calculations for clinical trials in the context of performance monitoring, they are typically set to be equal.

In addition, decision interval (h_0) on the CUSUM plot was calculated based on the variables mentioned previously, including acceptable and unacceptable failure rates and type I and type II errors(244-245).

When the CUSUM score decreased below the current decision level, the CUSUM score was replaced by the current decision level. If the CUSUM score exceeded the decision interval, in contrast, it indicated an unacceptable performance, and the CUSUM monitoring was then restarted at the next decision interval. The number of polyp observations and decision intervals required to reach a plateau for each trainee were identified by upward CUSUM plots.

The definition and calculations are explained here:

h_0 = amount of increment required to reach next decision level

S = amount subtracted for 'success'

$1 - S$ = amount added for ‘failure’

$$3. = \ln(p1/p0)$$

$$4. = \ln[(1-p0)/(1-p1)]$$

$$B = \ln[(1-\beta)/\alpha]$$

All statistical analysis was performed using Stata SE (Version 9.2, Statacorp, Texas, USA).

9.3 Results

9.3.1 Patient and polyp characteristics.

Four senior gastroenterology fellows in training, who were certified by the JAG UK as independent colonoscopists, performed the procedures. Four hundred and five procedures were included in the study and patients had a median age of 55 years with 67% of the patients being male. Table 37 summarises the main indications for lower GI investigations.

A total of 754 small polyps were detected during this period. Forty-five polyps (5.9%) were excluded from final analysis either due to non-retrieval or unsuitable for histopathological analysis. Hence, a total of 709 polyps (<10mm) were included in the analysis. The majority of the polyps were adenomas (n=364), with the remainder being HPs, SSA/Ps, cancer, or other polyp types (hamartomas, inflammatory polyps, or prominent normal colonic mucosa). Polyp characteristics and location are presented in table 38.

Table 36. Indications for colonoscopy and flexile sigmoidoscopy

Indication	Number	Percentage (%)
Rectal bleeding	46	11.3
PR bleeding + CIBH	12	3
CIBH	34	8.4
Imaging abnormality	9	2.2
Polyp surveillance	40	9.9

Indication	Number	Percentage (%)
Post CRC surveillance	11	2.7
FH CRC or polyposis	11	2.7
Abdominal pain	5	1.2
Screening	213	52.6
Colitis surveillance	6	1
Others	9	2.2

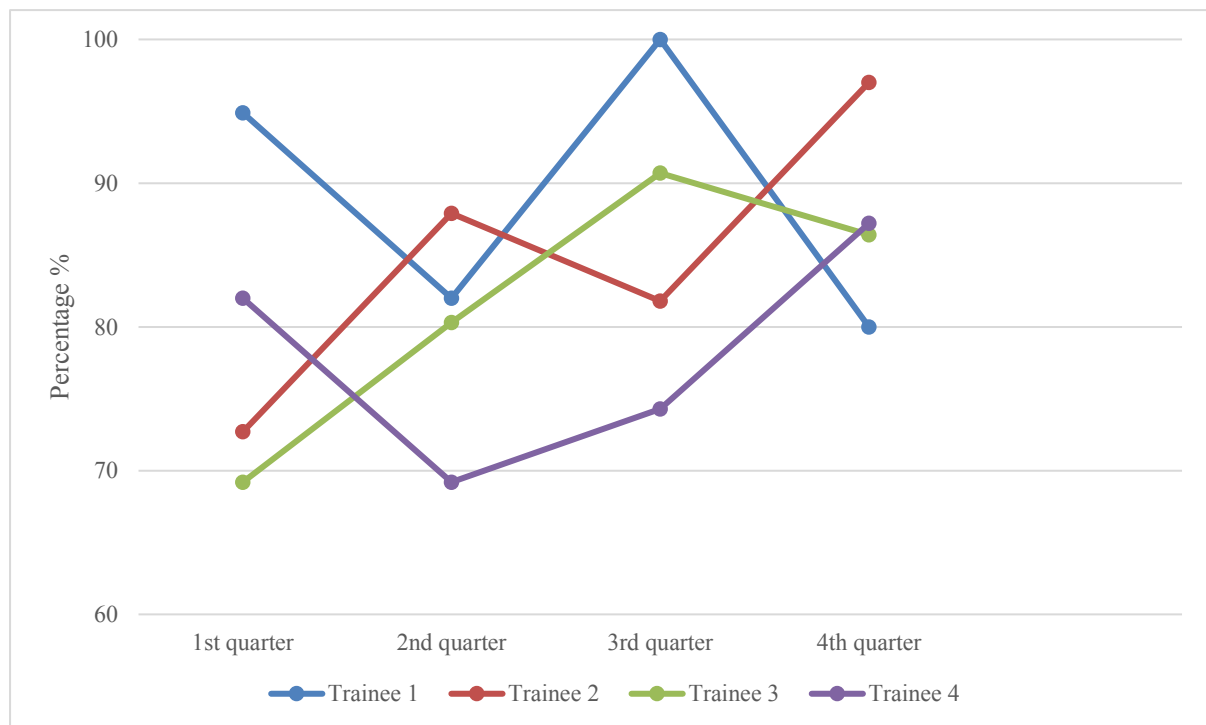
Table 37. Location and histological sub types of polyps

	Number
Polyps	709
Adenomas	364
Hyperplastic polyps	214
SSA/Ps	52
Cancer	2
Others	77
Location	
Caecum/appendix	32
Ascending colon	35
Hepatic flexure	8
Transverse colon	43
Splenic flexure	16
Descending colon	64
Sigmoid colon	284
Rectum	227

Table 39 summarises the optical diagnostic performance of all four trainees. The overall sensitivity and negative predictive value to differentiate adenomas from HPs were found to be between 92-95%. and 91-93% respectively. Figure 27 illustrates the accuracy of OD for all four trainees in each quarter of the study period.

Table 38. Optical diagnostic performance of trainees

Trainee Number	1	2	3	4
Sensitivity	95%	96%	94%	92%
Specificity	91%	87%	83%	91%
Positive Predictive Value	89%	94%	88%	94%
Negative Predictive Value	92%	92%	91%	93%

**Figure 27.** Accuracy of optical diagnosis in differentiating adenomas from HPs and SSA/Ps over the study period

9.3.2 CUSUM plots

Optical diagnostic accuracy and NPV of 90% were considered acceptable as defined by PIVI. Acceptable and unacceptable failure rates were set at 0.1 and 0.2, respectively. Subsequently, S and h0 were calculated based on above rates and type I and II errors by using the formulas described in the methods. S and h0 values were 0.145 and 2.71, respectively. CUSUM scores were then calculated based on S and 1-S dictated by the success of accurate prediction of optical

diagnosis. For trainee 1 and 2 the CUSUM score reached a plateau after 12 and 26 polyp observations. For trainee 3 it took 52 observations to achieve the plateau and to maintain the performance. Lastly for trainee 4, the CUSUM score initially attained the plateau after 24 polyp observations but, was not maintained and performance declined until finally achieved a plateau after 58 observations with subsequent maintenance of performance during the study period (figure 28).

Defined values:

p_0 = level of inherent error procedure calculated correctly = 0.1

p_1 = unacceptable failure rate = 0.2

α = 0.10

β = 0.10

Calculated values:

$$5. \quad = \ln(p_1/p_0) = \ln(0.2/0.1) = 0.693$$

$$6. \quad = \ln[(1-p_0)/(1-p_1)] = \ln(0.9/0.8) = 0.118$$

$$B = \ln[(1-\beta)/\alpha] = \ln(0.9/0.1) = 2.197$$

$$S = Q / (P+Q) = 0.118/(0.693+0.118) = 0.145$$

$$1 - S = 1 - 0.145 = 0.855$$

$$h_0 = b / (P+Q) = 2.197/(0.693+0.118) = 2.709$$

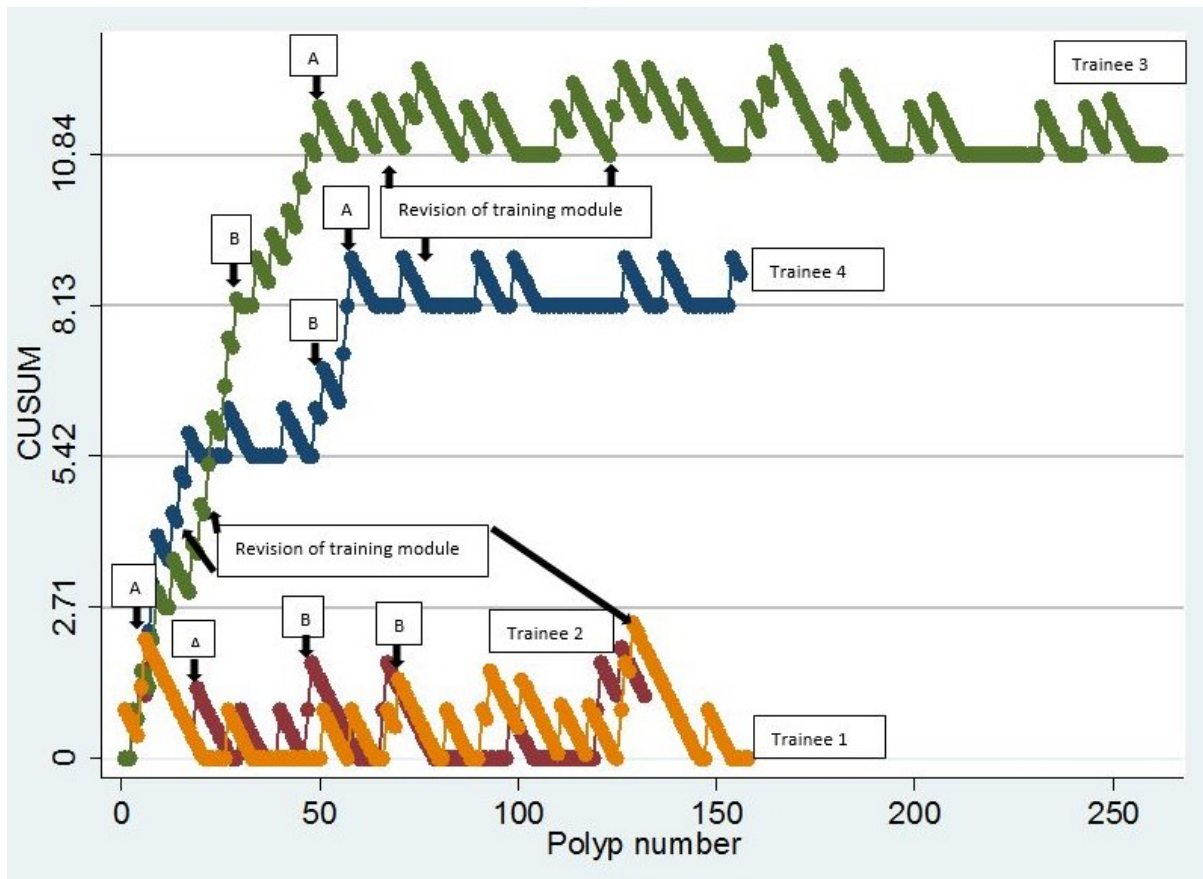


Figure 28. Upward CUSUM plots of trainees. A – Number of polyp observations needed to achieve plateau, B – in-vivo feedback during colonoscopy

9.4 Discussion

Recently ESGE endorsed that virtual and dye based chromoendoscopy can be used for real time optical diagnosis of diminutive colorectal polyps to replace gold standard histopathological diagnosis under strict controlled conditions with regular audit and quality assurances(139). The guidance emphasized that optical diagnosis can be safely performed but only by experienced endoscopists who are adequately trained in optical diagnosis, familiar with the common OD classification systems and able to document and quality assure the process (139). However, the ESGE identified that there is no universal training module in OD and that implementing OD with a DISCARD strategy in the longer term presents a significant challenge to the practising endoscopist.

Recently, two other studies explored the learning curve of optical diagnosis. Neither study highlighted the number of polyp observations required to reach the NPV thresholds (239,240). Moreover, only in one study, were the procedures performed by less experience endoscopists(240). Therefore, analysis of the learning curve for optical diagnosis of trainees or moderately experienced endoscopists, is necessary to determine the number of polyp observations to achieve and maintain PIVI thresholds(134).

For all four GI fellows, the learning curve reached a plateau within 58 polyp observations. These results indicate that with training in OD, acceptable performance can be achieved relatively quickly even in moderately experienced endoscopists. However, as expected some individuals require more time and training than others. This was highlighted

in the learning curve of trainee 4 who initially appeared to achieve the competence plateau after 24 polyp observations but who's performance decreased thereafter. Continuous performance monitoring appears important to ensure competency is maintained and the CUSUM graphical approach gives an easy to understand visual means of monitoring improvement (242,246).

Bae and colleagues published a study in which 15, less experienced endoscopists trained with WASP and NBI classifications (240). A total of 7294 polyps including 486 SSA/Ps were diagnosed in real time. Endoscopists achieved a NPV of 92% for diminutive neoplastic polyps and concordance surveillance interval of 90%. It was emphasized that re-education with ex vivo and in vivo feedback were necessary to maintain competency levels.

McGill and colleagues published a randomised multi-centre trial involving 5 endoscopists who were trained using a computer-based module prior to study commencement. For the 445 diminutive polyps detected, the NPV improved from 88% in the first half to 95.8% in the second half of the study period ($P=0.7$) (239). Concordance of post polypectomy surveillance intervals was assessed and was found to be identical between the two halves of the study, at

98%. All participating endoscopists completed a refresher course and continued training throughout the study period to maintain the desired levels of performance. One of the drawbacks of this study was that 60% of the endoscopists were experts in NBI. In contrast, in our study all endoscopists were trainees with limited exposure to NBI or similar virtual chromoendoscopy techniques.

The multi-centre, DISCARD 2 study, using an older NBI technology to our study, was designed to determine whether NBI-assisted optical diagnosis could be used in routine clinical practice outside academic centres (112). In this study, there were 915 diminutive polyps and non-expert endoscopists made high confidence optical diagnosis after training achieving from 49% to 72% for adenomatous lesions. NPV for diminutive polyps was just 64.5% overall. The main weakness in this study was that continuous assessment of competency and feedback were not applied during the trial.

Mc Gill et al(239), have recreated a useful graphic, Miller's pyramid, that demonstrates the steps in development of clinical skills (247), (figure 29). Applying this to optical diagnosis, at the base of the pyramid is acquisition of basic knowledge in OD, which can be provided by a learning module ("knows how"). Then, skills are acquired while performing optical diagnosis at colonoscopy under supervision with performance assessed against the gold standard of histology ("knows how"). Revision of the learning module and in-vivo feedback helps to build on the knowledge acquired to maintain performance levels. A trainee demonstrates that he/she could practice OD in day to day clinical practice with confidence. Finally, the clinical skill is audited in clinical practice with continuous feedback to ensure performance is maintained ("shows how" & "does").

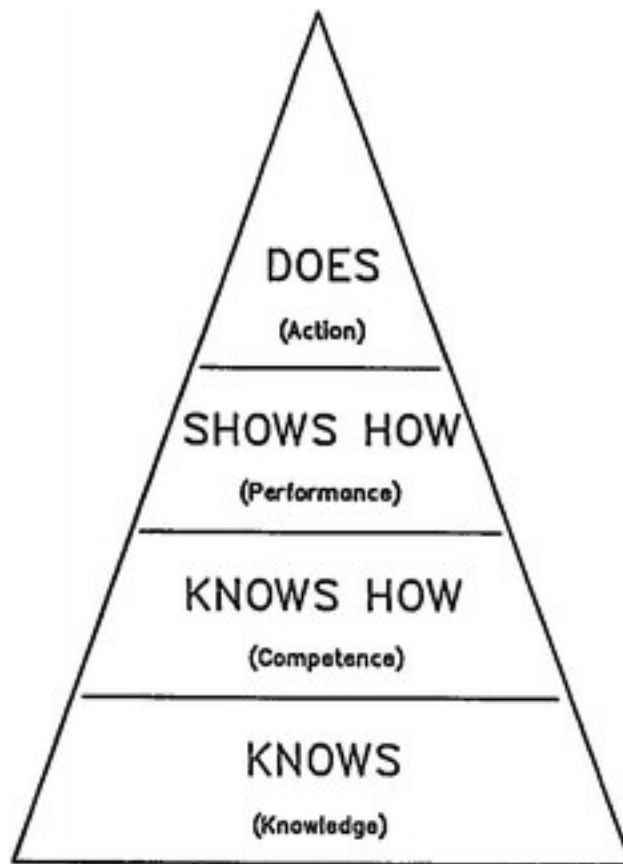


Figure 29. Millers pyramid for the assessment of competency of clinical skills .Adapted from Miller et al(247).

There are several strengths in this pilot study. Firstly, the participating endoscopists were less experienced endoscopists with limited experience in virtual chromoendoscopy. Hence, the findings are more applicable to routine clinical practice where skills and knowledge will be variable. Secondly, we have used the validated optical diagnostic scales of the NICE(110) and WASP classifications(138) and successfully shown that HP's can be differentiated from SSA/Ps. Thirdly, we have provided real time feedback on optical diagnostic performance, particularly applicable when there is a demonstratable drop in performance.

There were a few limitations to our study that need to be highlighted. Firstly, it was a single centre study assessing the performance of a limited number of trainees. Whether similar outcomes could be achieved in a larger group of trainee endoscopists remains to be seen.

Secondly, we did not measure the 2nd PIVI thresholds of surveillance interval (134) predicted by optical diagnosis as the procedures included colonoscopy and flexible sigmoidoscopy examinations. BSG guidelines suggest post polypectomy guidelines are applicable following a complete examination of the colon. International consensus suggests that both PIVI standards need to be fulfilled prior to wider implementation of OD in clinical practice. Thirdly, PIVI standards and ESGE guidelines suggest optical diagnosis could only be applied to diminutive polyps as the malignant potential/harboured advanced histology of small polyps is significantly greater than that of diminutive polyps. In a systematic review of 20,562 average risk patients undergoing screening colonoscopy showed that, 0.9% of patients with diminutive only lesions had an advanced adenoma and 0.04% had cancer(248). However both this study and the DISCARD1 study showed that the optical diagnosis could be extended to small polyps as well(249), provided high confidence diagnosis are made and appropriate training is provided.

In conclusion, our data shows the minimum number of polyp observations (n=58) needed to achieve and maintain competency in OD for trainee operators. A comprehensive and validated training module in association with in-vivo feedback and continuous revision of the learning module, were effective in maintaining competency, despite one of the 4 operators requiring additional training after initially demonstrating competence.

In the future artificial intelligent (AI) systems and computer aided diagnosis could provide even more robust assessment of optical diagnostic performance of individuals. Recent studies applying deep convolutional neural networks appear to be promising(143). An AI platform could accelerate the adoption of ‘resect and discard’ or ‘detect and disregard’ strategies for diminutive and probably for small colorectal polyps. However, even once such systems are available, individual colonoscopists will still bear the responsibility for OD calls so demonstrable competence in OD will become an essential core endoscopic skill.

Chapter 10

Conclusions and future directions

This thesis examined whether novel colonoscopic techniques can improve detection and in vivo characterisation of colorectal polyps. Although colonoscopy is considered as the gold standard diagnostic and therapeutic modality for colonic polyp management, there is a significant polyp miss rate which is likely to be responsible for about 52% of post-colonoscopy colorectal cancers (250). A major drawback of colonoscopy is the inability to visualise blind spots in colon such as the splenic and hepatic flexures and the proximal side of haustral folds. The prospective observational study to assess the polyp miss rate in a BCSP population in chapter 2 was performed by experienced, BCSP-accredited colonoscopists with high ADR's (>45%), overall polyp and showed that the adenoma miss rate even in experienced hands was significant. Furthermore, our study identified the high-risk groups for missed polyps (advanced age, history of multiple polyps and proximal colonic location). This chapter set the scene for further investigation of novel techniques to improve the visualisation of the colonic mucosa to improve polyp detection. A pre-clinical tandem detection study with the EWAVE system compared to standard colonoscopy showed that EWAVE significantly improved simulated polyp detection. Although the novel detection capability of the system was assessed the study was preclinical and did not allow evaluation of the therapeutic capability of the EWAVE scope. In future, clinical trials should assess both the detection capability and therapeutic practicality of the novel system.

DETECT was a randomised tandem study comparing two colonic distal attachments; cap and Endocuff Vision. Both devices have the potential to improve the visualisation behind colonic

folds. Our study demonstrated that EV appeared superior in detecting adenomas and SSA/Ps when compared to the cap. In addition, EV improved the efficiency of the procedure providing a controlled and enhanced view of colonic mucosa and prevents multiple to and fro movements. In addition, EV offers a stable platform to perform complex colonic polypectomy

INWARD was a prospective, randomised, parallel study conducted in bowel scope, during which the endoscopists carefully examined the mucosa during both the insertion and withdrawal phases of the examination. This trial concluded that additional meticulous examination on insertion during bowel scope examination did not result in an increase of ADR or MAP. Therefore, a well scrutinised inspection during withdrawal remains the cornerstone of a quality examination. Whether the results of this study can be translated to colonoscopy practice remain to be seen. Future multi centre studies in colonoscopy are probably warranted to assess whether there is any advantage at colonoscopy to a slower more detailed examination during insertion through the sigmoid.

There are many validated key performance indicators to assess the quality of colonoscopy. ADR is considered as the most reliable surrogate marker of PCCRC and it is widely used as a marker of colonoscopy quality(251). A study by Kaminski and colleagues showed that PCCRC rate was 10 times higher in colonoscopists with an ADR <20% compared to high detectors >20%)(10).However, it does not measure the number of adenomas detected in a given individual and does not measure the SSA/P detection rate. Furthermore, it does not assess the efficiency of an examination. We proposed a novel marker SP6 to assess colonoscopic efficiency and to compare the efficiency of two or more interventions. It includes the number of adenomas and SSA/Ps detected and resected in a given time. This marker needs to be validated in randomised, multi-centre trials comparing novel devices and interventions prior to wider adoption.

NBI has been widely adopted in colonoscopy practice for many years and there is an established classification system (NICE) for differentiation of neoplastic and non-neoplastic polyps. It is relatively easy to use and has been validated. BLI is a slightly newer technology using blue light imaging that also highlights surface structure and vascularity. Classification systems similar to NICE have been proposed (Hiroshima, BASIC) but are less user-friendly incorporating both morphological and vascular/surface pattern criteria. We wondered whether in fact the established NICE classification could be used for BLI in characterising polyps.

This design of the study, using still images was a practical way of assessing inter observer agreement by expert endoscopists. Our study appears to show that the NICE classification is equally applicable to BLI technology. However, prior to the adoption of the NICE classification for BLI, particularly when used for a resect and discard policy, these preliminary findings would need to be validated prospectively in clinical trials. However, having one universal classification system for distinguishing polyps makes a resect and disregard policy easier to adopt and follow, one remaining issue with “resect and disregard” is that SSP’s are recognised as precancerous lesions and should not be left in situ even if small and at the recto sigmoid. The ASGE and ESGE recommend that diminutive HPs at the recto-sigmoid can be left in situ without resection however, some lesions could be pre-cancerous SSA/Ps rather than simple hyperplastic polyps. Our retrospective review of screening colonoscopies and flexible sigmoidoscopies of 1000 consecutive patients showed that the prevalence of diminutive SSA/Ps in the recto sigmoid colon was incredibly low (2.8%). These results favour the safety and feasibility of ‘do not resect’ policy for hyperplastic appearing diminutive recto sigmoid polyps.

In Chapter 5 our data outlined the minimum number of high confidence polyp observations (i.e., 58 observations) needed to achieve and maintain competency in optical diagnosis for trainee operators. A comprehensive and validated training module, which incorporates NICE

and WASP classifications in conjunction with in-vivo feedback and self-learning were effective in maintaining competency. The CUSUM based methodology appears promising in assessing and demonstrating sustained performance above acceptable thresholds for adopting a resect and disregard strategy.

AI is an exciting new development in optical diagnosis(336). For the future, deep learning-based AI holds substantial potential to facilitate detection by highlighting areas of possible adenomatous or serrated mucosa for close inspection by the endoscopist. AI technology shows promising results to differentiate adenomas from HP polyps with >97% NPV(252). Incorporation of AI into widespread community clinical use will be challenging. Physicians and patients should gain confidence in the technology and should grow the trust in the exclusive decision-making capability of the system. Any novel technology should have minimal impact on the Endoscopist's working environment. AI is an adjunct in decision making to the endoscopist and the ultimate medico legal responsibility rests on the operators shoulder. Incorporation of AI into routine clinical endoscopic practice will be essential prior to the adoption and safe use(143). Furthermore, alternative endoscopic images such as confocal laser and endocytoscopy can potentially be used to train this platform to provide automatic interpretation of clinically acquired images.

In conclusion, advanced technologies such as extra wide-angle video colonoscope, disposable distal attachments (Endocuff Vision) showed great promise in improving polyp and adenoma detection. Novel marker SP6 appears to be promising to assess the efficiency of the colonoscopic procedures and novel interventions. Optical diagnosis using BLI is an exciting development and a welcome addition to the imaging armamentarium. Assessment using CUSUM could be used as a platform to assess and to monitor the competency of endoscopists in optical diagnosis. Training, novel technology and enhanced imaging technology transformed modern endoscopic practice. Research in endoscopic technology is growing every day,

However, the challenge of performing a complete and systematic endoscopic examination falls on the shoulder of individual endoscopist. With the exciting developments of artificial intelligence in endoscopy has the potential to improve the quality of colonoscopy at every level. It will compensate human errors, judgements, and limited capabilities by improving more consistency, speed and assist in endoscopic diagnosis/assessment, making the colonoscopy procedures more efficient and higher quality.

Chapter 11

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Appendix 1

Publications and presentations arising from the thesis

Full publications of manuscripts in peer reviewed journals

Rameshshanker R, Wilson A. Electronic Imaging in Colonoscopy: Clinical Applications and Future Prospects. *Curr Treat Options Gastroenterol*. 2016; 14: 140–151.

Rameshshanker R, Tsiamoulos Z, Wilson A, Rajendran A, Bassett, Tekkis P, et al. *Gastrointest Endosc* 2020 Apr;91(4):894-904.e1.

Rameshshanker R, Saunders BP. Number of significant polyps detected per six-minute withdrawal time at colonoscopy (SP6): a new measure of colonoscopy efficiency and quality. <http://dx.doi.org/10.1136/flgastro-2019-101184>

Published abstracts

Rameshshanker R, Wilson A, Tekkis P, Saunders BP.

Extra Wide-Angle View Colonoscope (EWAVE) has Superior Polyp Detection Rate When Compared to a Standard Colonoscope (SD): A Randomised Tandem Pre-Clinical Study. *Gut* 2016;65(1): A10

Extra Wide-Angle View Colonoscope (EWAVE) has Superior Polyp Detection Rate When Compared to a Standard Colonoscope (SD): A Randomized Tandem Pre-Clinical Study. *Gastrointest Endosc* 2016;83(5): AB405

Rameshshanker R, Purchiaroni F, wilson A, Rajendran A, Thomas- Gibson S, Humphries A, Haycock A, Suzuki N, Vance M, Saunders BP.

High levels of presumed polyp miss rate at 1- and 3-years following index screening colonoscopy: no room for complacency. *Gastrointest Endosc* 2017;85(5): AB417

High levels of presumed polyp miss rate at 1- and 3-years following index screening colonoscopy: no room for complacency. Gut 2016;66(2): A60-61

Rameshshanker R, Purchiaroni F, Wilson A, Thomas-Gibson S, Rajendran A, Tsiamoulos Z, Saunders BP.

Prevalence of sessile serrated adenomas/polyps in distal colon during colonoscopy/flexible sigmoidoscopy: a single bowel cancer screening experience from UK. Gut 2017;66(2): A225

Rameshshanker R, Wilson A, Tsiamoulos Z, Tekkis P, Saunders BP.

Number of Significant Polyps Detected Per Six Minutes of Withdrawal Time at Colonoscopy (SP6): A New Measure of Colonoscopy Efficiency and Quality. Gut 2016;65(1): A66-67.

Rameshshanker R, Wilson A, Thomas-Gibson S, Suzuki N, Tekkis P, Saunders BP.

NICE classification for optical diagnosis of colonic lesions is equally applicable when using blue laser imaging. Gut 2016;65(1): A66

Rameshshanker R, Wilson A, Thomas-Gibson S, O'shea N, Yusuf A, Saunders BP.

Learning curve for optical diagnosis of colorectal polyps using cumulative sum analysis. Gastrointest Endosc 2017;85(5): AB193

Learning curve for optical diagnosis of colorectal polyps using cumulative sum analysis. Gut 2017;66(1):A56

Rameshshanker R, Tsiamoulos Z, Wilson A, Saunders BP.

Endocuff assisted colonoscopy significantly improve ADR comparing to cap assisted colonoscopy: a randomised study (DETECT). Gut 2018;67(1):A38

Podium presentations

Expanding the horizons for early colorectal cancer

United European Gastroenterology Week, Barcelona, Spain 2019

Endocuff Vision: Improving adenoma detection at colonoscopy

British Society of Gastroenterology Endo Live, Newcastle, UK 2019

Hats on: When to use caps and cuffs

Frontiers, St Mark's Hospital and academic institute, London, UK 2018

Endocuff assisted colonoscopy significantly improves adenoma miss rate compared to cap assisted colonoscopy: randomised back to back study (DETECT)

Digestive Disease Week, Washington DC, USA, 2018

Missed colorectal polyps: no room for complacency

Grand round, St Mark's Hospital and Academic institute, London, UK, 2018

Endocuff assisted colonoscopy significantly improves adenoma detection rate compared to cap assisted colonoscopy: A randomised back to back study (DETECT)

United European Gastroenterology Week, Barcelona, Spain 2017

Extra wide-angle view colonoscope has superior polyp detection rate when compared to a standard colonoscope: a randomised tandem pre-clinical study

British Society of Gastroenterology annual meeting, Liverpool, UK 2017

Prevalence of sessile serrated adenomas/polyps in the distal colon during screening
colonoscopy/flexible sigmoidoscopy

United European Gastroenterology Week, Vienna, Austria 2016

Endoscopic cuff–assisted colonoscopy versus cap-assisted colonoscopy in adenoma detection: randomized tandem study—DEtection in Tandem Endocuff Cap Trial (DETECT)

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Background and Aims: Adenoma miss rate during colonoscopy is directly linked to risk of postcolonoscopy colorectal cancer. One of the reasons for missed adenomas is poor visualization of proximal folds during standard colonoscopy withdrawal. Disposable distal attachments such as the plastic cap and Endocuff (Arc Medical Design, Leeds, UK) that hold back folds appear to improve adenoma detection. The primary aim of this study was to compare adenoma detection rates between Endocuff-assisted colonoscopy (EAC) and cap-assisted colonoscopy (CAC).

Methods: This is a randomized, single-center, tandem colonoscopy trial performed by the same endoscopists on the same day, first with Endocuff Vision (Arc Medical Design, Leeds, UK) followed by cap or vice versa. All procedures were performed by 3 experienced gastroenterology fellows.

Results: One hundred fifty-four patients were recruited. Seventy-eight (50.6%) had CAC as their first procedure. Mean patient age was 61 years (male-to-female ratio, 1:1). Adenoma detection rate was significantly higher for EAC when compared to CAC (53% vs 26%, $P = .001$). Polyp miss rate was significantly lower in EAC (8.4%) compared with CAC (26.1%, $P < .001$) as was adenoma miss rate (EAC vs CAC, 6%, vs 19%; $P = .002$) and diminutive adenoma (<5 mm) miss rate in the EAC group (1.8% vs 19.6%, $P < .001$). However, there was no significant differences in the miss rates for small adenomas (5–9 mm) (3.7% vs 2.9%, $P = .69$) or adenomas 10 mm or larger (1.6% vs 2.6%, $P = .98$). The mean number of adenomas per procedure was significantly higher with EAC compared with CAC (1.5 vs .8, $P < .001$). Cecal intubation time was significantly shorter with EAC than CAC (median 6 vs 7 minutes, $P = .01$). Conversely, withdrawal time (median 10 vs 8 minutes, $P = .01$) was significantly longer in EAC.

Conclusions: This randomized, tandem study demonstrates that EAC has a significantly higher adenoma detection rate and lower adenoma miss rate than CAC. Although insertion times were shorter with EAC, procedures were slightly more uncomfortable, and the cuff had to be removed in a small number of cases. (Clinical trial registration number: NCT 03254498.) (Gastrointest Endosc 2020;91:894-904.)

(footnotes appear on last page of article)

Colonoscopy with adenoma detection and removal is established as the optimal way of preventing colorectal cancer (CRC). However, adenomas can be missed during colonoscopy inspection even when the procedure is performed by experienced endoscopists,¹ and the adenoma

detection rate (ADR) has been shown to be an independent predictor of the risk of interval CRC after screening colonoscopy.^{2–5} Reasons for lesions not being detected at colonoscopy include suboptimal technique; shorter withdrawal time (WT); inadequate bowel preparation; presence of flat, depressed, or subtle lesions; and the inability to visualize the proximal side of haustral folds or flexures.^{6,7} Optical imaging innovations and technologic developments in the field of colonoscopy have attempted to decrease the adenoma miss rate (AMR) with the introduction of high-definition endoscopes, electronic chromoendoscopy (such as narrow-band imaging), wide-angle colonoscopes, retrograde viewing devices, and



Use your mobile device to scan this QR code and watch the author interview. Download a free QR code scanner by searching “QR Scanner” in your mobile device’s app store.

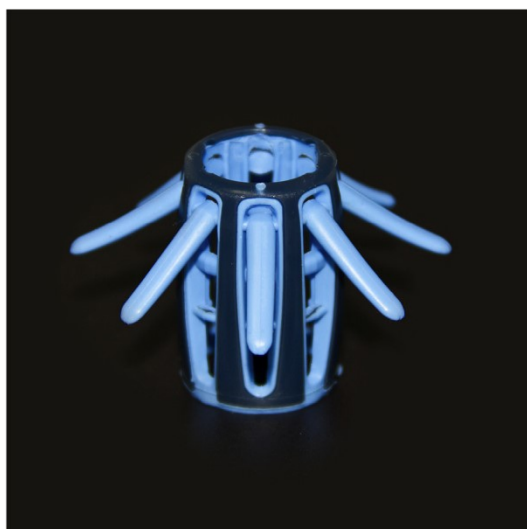


Figure 1. Endocuff Vision.

adjunct disposable distal attachments.^{8,9} Views may also be improved with dynamic patient position changing and routine retroflexion.^{10,11}

Studies involving relatively simple, disposable distal attachment devices (cap, Endocuff, and Endorings, EndoAid Ltd, Caesarea, Israel) have shown benefits compared with standard colonoscopy (SC).¹²⁻¹⁵ Several randomized controlled trials highlighted the impact of Endocuff on ADR including the largest ADENOMA trial with Endocuff Vision (EV [Arc Medical Design, Leeds, UK]; Figs. 1 and 2). This study showed an increment in ADR to 10% in a bowel cancer screening population.¹⁶⁻²¹ Cap-assisted colonoscopy (CAC; Figs. 3 and 4) trials have been rather heterogenous and report mixed results to date,¹²⁻¹⁴ but the cap has also been reported to make insertion easier. Tandem studies in which each patient undergoes back-to-back colonoscopies on the same day have been used to evaluate AMR between a new device or technology and conventional colonoscopy,^{22,23} and we used a similar study design to compare the 2 most promising distal attachment devices to date: the EV and the straight plastic cap (disposable distal attachment; Olympus, Tokyo, Japan).

METHODS

Study design

A prospective, randomized, tandem study was conducted between April 2016 and May 2017 in a single endoscopy unit in the United Kingdom. The DETection in Tandem Endocuff Cap Trial (DETECT) protocol was reviewed and approved by the East of England (Cambridge) ethics committee on the January 4, 2016 (Reference 15/EE/0415). The study was registered with clinical [trial.gov](https://clinicaltrials.gov/ct2/show/study/NCT03254498) (NCT03254498).



Figure 2. Endocuff Vision was snugly attached to the distal end of a colonoscope.

and International Standard Randomized Controlled Trials (ISRCTN 58994883).

Participants

Patients older than 18 years and referred for a colonoscopic examination via the symptomatic pathway at our institution were invited to participate in the study. Patients with the following conditions or pathology were excluded: established or suspected large-bowel obstruction, known CRC or polyposis syndrome, previous diagnosis of colonic stricture or severe diverticular disease, active colitis, patients on anticoagulants or antiplatelets that could not be stopped preprocedure or attending an elective therapeutic procedure, and pregnancy. Few ($n = 10$) invited patients were not enrolled because of logistical reasons or procedure cancellation.

Endoscopists

Three experienced endoscopists who had performed more than 1500 colonoscopies and who had experience in using both cap and EV (>20 cases for each device) participated in this trial. All endoscopists were senior GI fellows who were certified by the Joint Advisory Group on GI Endoscopy UK to perform colonoscopy procedures and polypectomies independently.

Colonoscopy procedures

All patients had a standard bowel preparation either with senna (10 tablets) and 2 sachets of magnesium citrate (Citramag; Sanochemia Diagnostics UK Ltd, Bristol, UK) or 2 sachets of Moviprep (macrogol and ascorbic acid; Norgine, Amsterdam, The Netherlands). Patients with suboptimal bowel preparation were cleaned using copious amount of water to achieve adequate mucosal inspection. Patients

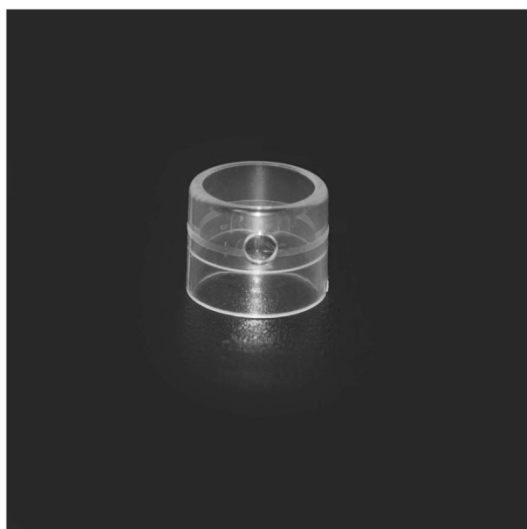


Figure 3. Transparent cap.

with poor bowel preparation (semisolid stools that could not be suctioned or washed away) were excluded. High-definition colonoscopes (CF-H260DL, PCF-H290ZL/I, or CF-H290L; Olympus) with Lucera video processors (Olympus) were used for all procedures. Detected polyps were either resected or underwent biopsy sampling, and the samples were sent for histopathology.

Definition of outcomes

ADR was defined as the proportion of patients in whom at least 1 adenoma (histologically proven) was detected. A polyp was determined to be missed if it was detected only during the second procedure. When an adenoma was detected only during the second colonoscopy, it was defined as a missed adenoma. AMR was defined as the proportion of missed adenomas among the total number of adenomas detected during the first and second procedures. Mean adenomas per procedure (MAP) is the average number of adenomas detected per colonoscopy procedure. WT was defined as the total WT, which includes inspection time and time taken to resect the polyps (polypectomy time).

Randomization

A computer-generated randomized sequence was used to assign patients to undergo tandem colonoscopies with either CAC or Endocuff-assisted colonoscopy (EAC) performed first. A concealed envelope containing the randomization sequence was opened only after informed written consent from the patients was taken. The first procedure was followed immediately by the second device-assisted colonoscopy and was performed by the same endoscopist.

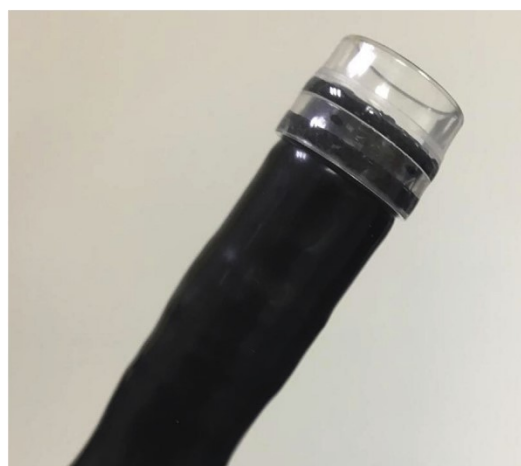


Figure 4. The cap was attached firmly to the tip of a colonoscope, and 4-mm length projected beyond the tip.

Outcomes

The primary aim was to compare ADR between EAC and CAC. Secondary outcome measures were to compare the MAP between EAC and CAC; to ascertain the miss rates for polyps, adenomas, advanced adenomas, sessile serrated adenomas/polyps (SSAs/Ps), and CRC; to compare the cecal intubation time (CIT) and WT between EAC and CAC; to demonstrate any difference in comfort score, including degree of discomfort on anal intubation; and to compare the number of dynamic position changes (DPCs) needed to achieve a satisfactory mucosal view between EAC and CAC.

Patient comfort score was assessed by a validated nurse assessment tool (1, completely comfortable; 2, minimal discomfort; 3, mild discomfort; 4, moderate discomfort; 5, severe discomfort) and patient questionnaires. Patients were followed for 21 days after the procedure, and any adverse events were collected and reported.

Statistical analysis

Sample size calculation. The study was powered to detect a difference in the ADR (primary outcome) between EAC and CAC. Preliminary work performed by the chief investigator suggested that a 10% increase in ADR is possible with EV when compared with SC. A recent meta-analysis of CAC versus SC showed no difference in ADR. We hypothesized that the performance of CAC would be very similar to SC. A 10% difference in ADR was considered clinically significant. ADR for symptomatic patients who underwent a colonoscopy at our institution was 16% (unpublished data, St Mark's Hospital, 2015). Therefore, to demonstrate a 10% difference in ADR with a 5% significance level and 90% power using a 2-sided test, the sample size was calculated as 154 patients per group.

Analysis. Demographic and baseline variables were summarized descriptively for the 2 study arms separately. No formal hypothesis tests were used to compare the 2 groups for these measures. All efficacy analyses were compared between the 2 groups for each procedure separately.

Continuous variables were summarized median or mean and standard deviation/interquartile range. The exception to these rules was for MAP and other polyp/adenoma detection outcomes and miss rates, which were summarized as mean and standard deviation, regardless of the data distribution. Categorical variables were summarized by the frequency and percentage of values in each category.

The primary outcome, ADR, was calculated using the χ^2 test. Two-sided *P* values were reported, along with 95% confidence intervals for the mean difference between groups. All secondary outcome analyses were performed for data from the first and second procedure separately. For each procedure, the χ^2 test was used to compare this outcome between groups. Several secondary outcomes including AMR were analyzed using the Mann-Whitney test. The number of position changes were found to be approximately normally distributed, and the Student unpaired *t* test was used to compare between groups for each procedure.

RESULTS

Three hundred eighteen patients were invited to participate in the study. One hundred sixty-four patients were excluded because they either did not meet the inclusion criteria (55%) or declined to undergo tandem colonoscopies on the same day (39%). We recruited 154 patients (mean age, 61.3 ± 13.6 years) with equal sex distribution (men, 51%), and the trial flow chart is shown in Figure 5. Main indications for a colonoscopy were adenoma surveillance (28%), recent change in bowel habits (21%), family history of CRC (16%), and rectal bleeding (10%). No patients were lost to follow-up. Patient characteristics are summarized in Table 1.

All procedures were complete to the cecum during CAC. However, during EAC, 6.6% of colonoscopies (10/152) were not completed. Five procedures were not completed during the first pass because of moderate discomfort and severe diverticulosis with fixed and angulated sigmoid colon. During the second pass, 5 procedures were not completed with the Endocuff because 2 patients refused to undergo the second examination, and in 3 cases a fixed and angulated sigmoid colon could not be negotiated. All patients were included in the analysis and were followed for 21 days as per protocol.

Primary outcome: ADR

When we compared the first pass with EV or cap, there was a significantly higher ADR in the EAC arm ($P = .001$).

The results showed that at least 1 adenoma was detected in 26% of patients in the CAC group, compared with 53% in the EAC group. This gives a difference in ADR of 27% between groups. A very significant difference was also found when considering data from the second procedure, where the ADR was 9% in CAC group compared with 29% in EAC group (Table 2). Adenoma prevalence by size and location are shown in Table 3.

Secondary outcomes

Adenoma miss rate. The AMR was significantly lower in EAC (6%) when compared with CAC (19%, $P = .002$). A more-pronounced effect was noted for diminutive (<5 mm) adenomas, 1.8% for EAC and 19.6% for CAC. There was no statistically significant difference in SSAs/Ps or advanced AMR (Table 4).

Total number of polyps/adenomas and MAPs per procedure. When we analyzed the findings of the first procedure, the MAP was significantly higher ($P < .001$) in EAC compared with CAC. MAP was .6 in the CAC arm, rising to 1.5 in the EAC arm, with a mean difference of .8 between groups (Table 5).

There were significant differences between EAC and CAC in terms of the detection of diminutive adenomas (≤ 5 mm) and larger adenomas (>10 mm), but no difference was found for small adenomas (6-9 mm). Detection of diminutive adenomas was 42% in the EAC group but only 15% in the CAC group ($P < .001$). Detection of large adenomas was 17% in the EAC group but only 4% in the CAC group ($P = .007$). There was no significant difference in the number of small adenomas between both groups ($P = .37$).

There was a significantly higher detection rate in the EAC group (21%) compared with only 4% in the CAC group ($P = .001$) for advanced adenomas (adenomas >10 mm, villous histology, or high-grade dysplasia). There was no significant difference in the detections of SSAs/Ps between both arms ($P = .96$). CRC was rare and detected only in 3 patients. A very similar trend was observed during the second procedure. These findings are summarized in Table 6.

Cecal intubation and WTs. Cecal intubation rate was 100% in the CAC group when compared with 93.5% in the EAC group. This is because in 10 patients (first and second procedures combined) the Endocuff was removed to complete the examination. The results suggested that during both procedures, CITs were lower in the EAC group compared with CAC (Table 7). CIT was a median of 1 minute shorter in the EAC group during the first procedure ($P = .01$) and a median of 2 minutes shorter in the second procedure ($P = .05$).

Conversely, WT was significantly longer in the EAC group in the first procedure ($P = .01$). The median difference was 2 minutes between groups. However, there was no significant difference in WT during the second procedure ($P = .47$). When negative WT was analyzed (patients where no polyps were detected or resected), there were no significant

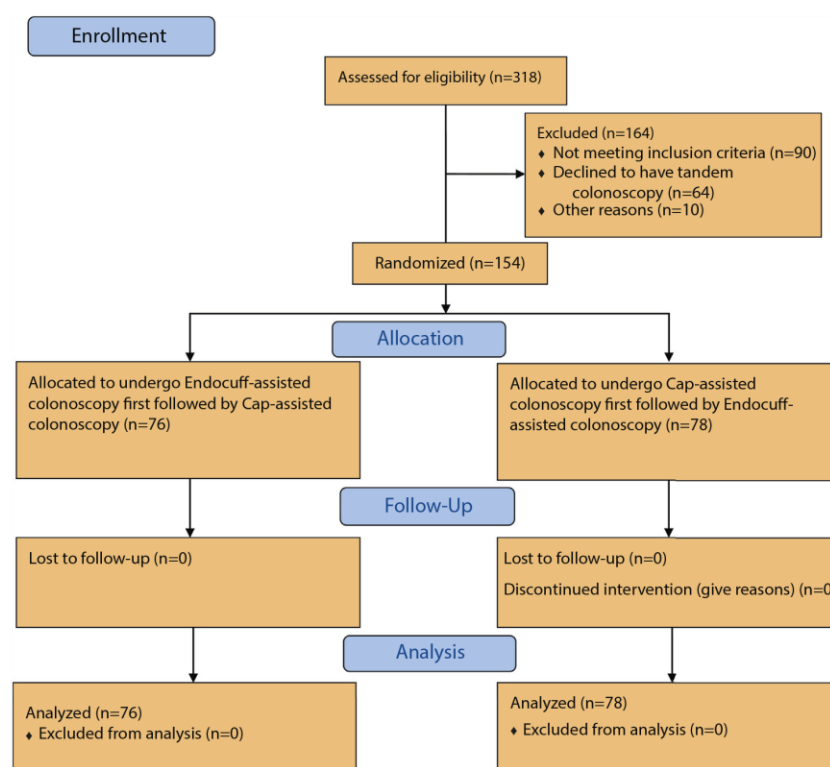


Figure 5. Consolidated Standards of Reporting Trials (CONSORT) study design.

differences between the 2 groups during the first or second procedures (median of 6 minutes each, $P = .37$).

DPC and patient experience. Number of DPCs during insertion and withdrawal were compared between groups, with the results summarized in [Supplementary Table 1](#) (available online at www.giejournal.org). During insertion, there were significantly fewer changes in the EAC group ($P < .04$) for the first procedure. The mean number of changes was 2.3 in the CAC group compared with 2.0 in the EAC group. There was no significant difference in DPC when performing colonoscopic insertion during the second procedure ($P = .47$). The number of DPCs during withdrawal was significantly lower in the EAC group for both the first ($P < .001$) and second procedure ($P < .001$). The number of changes were reduced in the EAC group by .9 per patient for the first procedure and 1.0 per patient for the second procedure.

Overall, patients tolerated tandem colonoscopic procedures with 2 different devices very well. Ninety-four percent of patients in the EAC group and 91% of patients in the CAC group had a “completely comfortable examination” or just “minimal discomfort” during the procedure ([Supplementary Table 2](#), available online at www.giejournal.org).

A total of 6.4% of patients in the EAC group and 4% in the CAC group reported mild to moderate discomfort during anal intubation. There were no adverse events reported either during the procedure or within the 21-day follow-up period.

DISCUSSION

This is the first tandem, crossover, randomized trial to compare EAC with CAC. The primary aim was to compare ADR, and our results highlighted that EAC significantly improved detection of adenomas by 27% compared with CAC ($P = .001$). The total number of polyps detected by EAC was significantly higher than that detected by CAC (153 vs 58, $P < .001$). Furthermore, EAC improved the detection of missed adenomas by 13% (EAC, 6%; CAC, 19%) and SSAs/Ps by 3% compared with CAC. Our findings were consistent with the miss rate of other tandem studies comparing CAC against SC. A study performed by Hewett and Rex²⁴ recruited 100 patients and the reported AMR for CAC was 21%. The clinical significance of the significantly improved detection of diminutive polyps and adenomas (<5 mm) with EAC is unknown because of the low malignant potential of these lesions; however,

TABLE 1. Patient characteristics

Characteristic	Both groups (n = 154)	Cap-assisted colonoscopy first (n = 78)	Endocuff-assisted colonoscopy first (n = 76)	P value
Sex				
Male	79 (51.3)	43 (55.1)	36 (47.4)	.54
Female	75 (48.7)	35 (44.9)	40 (52.6)	.61
Mean age, y (standard deviation)	61.3 (13.6)	60.8 (12.6)	61.9 (14.7)	.81
Body mass index				
<20 kg/m ²	15 (9.9)	11 (14.3)	4 (5.3)	.04
20-30 kg/m ²	93 (61.2)	48 (62.3)	45 (60.0)	.72
>30 kg/m ²	44 (29.0)	18 (23.4)	26 (34.7)	.32
Indication*				
PR bleeding	15 (9.7)	10 (12.8)	5 (6.6)	.08
CIBH	32 (20.8)	17 (21.8)	15 (19.7)	.62
PR bleeding + CIBH	7 (4.6)	3 (3.9)	4 (5.3)	.45
Family history of CRC	25 (16.2)	13 (16.7)	12 (15.8)	.86
Polyp surveillance	43 (27.9)	18 (23.1)	25 (32.9)	.12
IDA	11 (7.1)	8 (10.3)	3 (4.0)	.1
Family history of CRC + polyp surveillance	12 (7.8)	6 (7.7)	6 (7.9)	.94
Post-CRC surveillance	10 (6.5)	5 (6.4)	5 (6.5)	.96
Abdominal pain + CIBH	8 (5.2)	4 (5.1)	4 (5.2)	.95
Colitis surveillance	8 (5.2)	4 (5.1)	4 (5.3)	.95
Weight loss	6 (3.9)	4 (5.1)	2 (2.6)	.34

Values are n (%) unless otherwise defined.

CRC, Colorectal cancer; PR, per rectal; CIBH, change in bowel habits; IDA, iron deficiency anemia.

*One patient may have multiple indications.

TABLE 2. Comparison of adenoma detection rate between both arms

Procedure	Adenomas detected	Cap-assisted colonoscopy	Endocuff-assisted colonoscopy	Difference (95% confidence interval) (%)	P value
1	No	58 (74.4)	36 (47.4)		
	Yes	20 (25.6)	40 (52.6)	27.0 (12.1-41.8)	.001
2	No	69 (90.8)	55 (71.4)		
	Yes	7 (9.2)	22 (28.6)	19.4 (7.4-31.4)	.002

Values are n (%).

improved detection of such polyps potentially parallels an improvement in larger polyp detection with EAC. Our study did not show lower miss rates for advanced adenomas ($P = .98$), but detection of adenomas larger than 5 mm ($P = .69$) and SSAs/Ps ($P = .25$) did improve. However, the rate failed to reach statistical significance.

Initial studies performed in Asia showed improved cecal intubation rates, intubation times, and ADR with CAC when compared with SC.^{12,25,26} However, a study described by Pohl et al²⁷ randomized 1113 patients to undergo CAC and SC and showed no difference in ADR (42% vs 40%; $P = .452$).

In contrast to the CAC studies, most trials evaluating the original Endocuff and EV against SC have showed significant improvements in ADR. An initial pilot study using EV showed a 16% improvement in ADR in a screening population.¹⁹ The ADENOMA study randomized 1772 patients to undergo EAC and SC and showed a 10.8% increment in ADR in a bowel cancer screening population.²¹

This study showed a 27% increment in ADR for EAC when compared with CAC. For an ADR calculation we compared the first procedures of EAC and CAC. This level (27%) of ADR increase is significantly higher than previously described EAC studies. These higher rates might

TABLE 3. Prevalence of adenomas per size and location

	Cap-assisted colonoscopy (n = 78)	Endocuff-assisted colonoscopy (n = 76)	Difference (95% confidence interval) (%)	P value
≤5 mm	12 (15.4)	32 (42.1)	26.7 (13.0-40.4)	<.001
6-9 mm	13 (16.7)	17 (22.4)	5.7 (-6.8 to 18.2)	.37
10+ mm	3 (3.9)	13 (17.1)	13.3 (3.8-22.7)	.007
Rectum	1 (1.3)	4 (5.3)	4.0 (-1.6 to 9.6)	.16
Sigmoid colon	8 (10.3)	18 (23.7)	13.4 (1.7-25.1)	.03
Descending colon	3 (3.9)	6 (7.9)	4.0 (-3.3 to 11.4)	.28
Splenic flexure	2 (2.6)	7 (9.2)	6.6% (-7 to 14.0)	.08
Transverse colon	7 (9.0)	10 (13.2)	4.2% (-5.7 to 14.1)	.41
Hepatic flexure	2 (2.6)	15 (19.7)	17.2% (7.6-26.7)	<.001
Ascending colon	3 (3.9)	9 (11.8)	8.0% (-4 to 16.4)	.06
Cecum	6 (7.7)	9 (11.8)	4.1 (-5.2 to 13.5)	.39

Values are n (%) unless otherwise defined.

TABLE 4. Comparison of adenoma miss rate in tandem colonoscopy

Polyp histology and size	Cap-assisted colonoscopy (n = 78) (%)	Endocuff-assisted colonoscopy (n = 76) (%)	Mean difference (95% confidence interval)	P value
Adenomas (any size)	19.0	6.0	-13.0 (-22.1 to -3.8)	.002
Adenoma ≤5 mm	19.6	1.8	-17.8 (-26.5 to -9.1)	<.001
Adenoma 6-9 mm	2.9	3.7	.9 (-4.4 to 6.2)	.69
Adenoma >10 mm	2.6	1.6	1.0 (-3.5 to 5.5)	.98
Polyps (any size)	26.	8.4	-17.7 (-27.3 to -8.0)	<.001
Polyps ≤5 mm	24.4	4.3	-20.2 (-29.2 to -11.1)	<.001
Polyps 6-9 mm	3.7	6.1	-2.4 (-8.8 to 4.1)	.52
Polyps >10 mm	2.6	.8	1.9 (-1.9 to 5.7)	.97
Cancer	.0	.0	*	
Advanced adenoma	4.2	4.6	.4 (-6.0 to 6.8)	.98
Sessile serrated polyp	4.9	1.8	-3.1 (-8.3 to 2.1)	.25

*No hypothesis test performed because of no missed cancers.

represent improved performance in a trial setting. Another potential explanation for this disparity could be because of the genuinely improved performance by EV in less-experienced endoscopists because the interventionalists were GI fellows in training who had performed just over 1500 colonoscopies.

A meta-analysis of CAC and SC analyzed 23 randomized control trials and 12,947 patients reporting a significantly shorter CIT (median, .82 minutes; 95% confidence interval, -1.20 to -.44; $P < .01$).²⁸ Similarly, studies using EV showed a shorter CIT. Initial pilot and ADENOMA studies both showed a median reduction of 1 minute when compared with SC.^{19,21} Our study reported significantly quicker CIT for both devices when compared with other studies using cap and Endocuff (median of 6 minutes for EAC and 7 minutes for CAC). CIT for EAC was significantly shorter than CAC (median difference, 1 minute; $P = .01$).

The difference could be because of easy maneuverability of the single set of softer and longer projections of EV and the ability to stabilize the endoscope tip during scope-straightening maneuvers, especially in long, capacious, and mobile colon. In addition, the number of DPCs needed to reach the cecum was far less than the SC.

The WT for EAC was slightly prolonged compared with CAC for the first procedure (median, 2 minutes; $P = .01$) but equivalent for both groups during the second procedure. In our study we measured the total WT (time spent on inspection + polypectomy time). One might argue that prolonged WT is associated with increased ADR in EAC. We conducted a subgroup analysis of WT in which 1 or more polyps was resected and showed no difference in WT (EAC vs CAC, 10.5 vs 11 minutes; $P = .12$). Furthermore, in procedures where no polyps were detected the WTs were similar (EAC vs CAC, 6 minutes each). The

TABLE 5. Mean number of polyps/adenomas per patient: first and second procedure

Polyp histology and size	Cap-assisted colonoscopy (n = 78)	Endocuff-assisted colonoscopy (n = 76)	Mean difference (95% confidence interval)	P value
First procedure				
Adenomas (any size)	.64 (1.77)	1.46 (2.65)	.82 (.10-1.54)	<.001
Adenoma ≤5 mm	.32 (.95)	.75 (1.41)	.43 (.05-.81)	<.001
Adenoma 6–9 mm	.24 (.67)	.34 (.78)	.10 (–.13 to .33)	.36
Adenoma 10+ mm	.06 (.37)	.37 (1.33)	.30 (.00-.61)	.007
Polyps (any size)	1.17 (1.99)	2.13 (3.28)	.96 (.10-1.83)	.007
Polyps ≤5 mm	.64 (1.14)	1.25 (1.78)	.61 (.13-1.08)	.01
Polyps 6–9 mm	.38 (.84)	.42 (.87)	.04 (–.24 to .31)	.76
Polyps 10+ mm	.13 (.47)	.46 (1.46)	.33 (–.01 to .68)	.03
Advanced adenoma	.09 (.49)	.49 (1.48)	.40 (.05 to .75)	.001
Sessile serrated polyp	.10 (.35)	.16 (.57)	.06 (–.09 to .20)	.91
Second procedure				
Adenomas (any size)	.13 (.47)	.45 (.88)	.32 (.10-.55)	.002
Adenoma ≤5 mm	.04 (.26)	.39 (.78)	.35 (.16-.54)	<.001
Adenoma 6–9 mm	.05 (.22)	.04 (.19)	–0.01 (–.08 to .05)	.69
Adenoma 10+mm	.03 (.16)	.03 (.16)	.00 (–.05 to .05)	.99
Polyps (any size)	.18 (.51)	.81 (1.34)	.62 (.30-.95)	<.001
Polyps ≤5 mm	.09 (.33)	.70 (1.28)	.61 (.31-.91)	<.001
Polyps 6–9 mm	.05 (.22)	.08 (.27)	.03 (–.05 to .10)	.53
Polyps 10+mm	.03 (.16)	.03 (.16)	.00 (–.05 to .05)	.99
Advanced adenoma	.07 (.30)	.06 (.30)	–0.01 (–.10 to .09)	.98
Sessile serrated polyp	.03 (.16)	.12 (.49)	.09 (–.03 to .21)	.24

Values are mean (standard deviation) unless otherwise defined.

primary reason for this difference is probably that significantly more polyps were detected and resected when the procedure was performed with EV (total number of polyps resected were 83 and 52 for EAC and CAC, respectively). This is a significant finding and shows the efficiency of the EV when performing diagnostic and therapeutic procedures. First, EV helps to improve the mucosal examination by holding back and everting the haustral folds, allowing the endoscopist to visualize the proximal side of the folds, which helps to improve polyp detection.²¹ Second, the finger-like projections help to withdraw the colonoscope in a controlled manner and prevents rapid slippage of the scope, hence minimizing the need for repeated “to and fro” movements to completely visualize the mucosa, especially at the flexures. Finally, EV provides a stable platform to perform multiple polypectomies and retrieval of polyp fragments, making the process time efficient.¹⁹ This observation was documented in recent Endocuff studies.^{19,21,29-31}

Another example of improved efficiency of EV was evident from the smaller number of DPCs that were needed during insertion (median 2 and 2.3 for EAC and CAC, respectively; $P = .04$) and withdrawal (2.4 and 3.3 for EAC and CAC, respectively; $P < .001$) to complete the examination. When colonoscopy is performed under

deep sedation, it would be greatly beneficial because multiple position changes are cumbersome.

Efficiency of an intervention or device cannot be correctly measured by routine key performance indicators such as ADR, cecal intubation rate, and WT. Therefore, we proposed a new metric to compare the efficiency of devices and interventions in colonoscopy: significant polyps detected and resected in a standard 6-minute WT.³² Significant polyps were defined as adenomas and SSAs/Ps because both histologic subtypes of polyps have neoplastic potential:

$$SP6 = \frac{\text{Total number of adenomas and SSA/Ps} \times 6}{\text{Procedure WT}}$$

where SP6 means significant polyps detected in 6 minutes of withdrawal. When we applied this formula to this study, significant polyps detected in 6 minutes of withdrawal for EAC and CAC were .64 and .23, respectively. This means that when performing EAC, .6 significant polyps per 6 minutes of WT and .2 polyps with CAC would be detected and treated during the same time period. This finding highlights that EAC is 3 times more efficient in detecting and treating polyps than CAC ($P < .001$).

When compared with previous studies, mucosal abrasions or undocking of the devices were not noted in this

TABLE 6. Adenoma/polyp characteristics per patient: first and second procedure

Polyp histology and size	Cap-assisted colonoscopy (n = 78)	Endocuff-assisted colonoscopy (n = 76)	Difference (95% confidence interval) (%)	P value
First procedure				
Adenoma ≤5 mm	12 (15.4)	32 (42.1)	26.7 (13.0-40.4)	<.001
Adenoma 6–9 mm	13 (16.7)	17 (22.4)	5.7 (–6.8 to 18.2)	.37
Adenoma 10+ mm	3 (3.9)	13 (17.1)	13.3 (3.8-22.7)	.007
Polyps ≤5 mm	31 (39.7)	41 (54.0)	14.2 (–1.4 to 29.8)	.08
Polyps 6–9 mm	19 (24.4)	20 (26.3)	2.0 (–11.8 to 15.7)	.78
Polyps 10+ mm	7 (9.0)	16 (21.1)	12.1 (9-23.2)	.04
Cancer	2 (2.6)	1 (1.3)	*	
Advanced adenoma	3 (3.9)	16 (21.1)	17.2 (7.1-27.3)	.001
Sessile serrated polyp	7 (9.0)	7 (9.2)	.2% (–8.8 to 9.3)	.96
Second procedure				
Adenoma <5 mm	2 (2.6)	20 (26)	23.3 (12.9–33.8)	<.001
Adenoma 6–9 mm	4 (5.3)	3 (3.9)	–1.4 (–8.0 to 5.2)	.69
Adenoma 10+ mm	2 (2.6)	2 (2.6)	.0 (–5.1 to 5.0)	.99
Polyps <5 mm	6 (7.9)	28 (36.4)	28.5 (16.1-40.8)	<.001
Polyps 6–9 mm	4 (5.3)	6 (7.8)	2.5 (–5.3 to 10.3)	.53
Polyps 10+ mm	2 (2.6)	2 (2.6)	.0 (–5.1 to 5.0)	.99
Cancer	0 (.0)	0 (.0)	*	
Advanced adenoma	4 (5.3)	4 (5.2)	–.1 (–7.1 to 7.0)	.99
Sessile serrated polyp	2 (2.6)	5 (6.5)	3.9 (–2.7 to 10.4)	.25

Values are n (%) unless otherwise defined.

*No hypothesis test was performed as there were no missed cancers.

TABLE 7. Comparison of cecal intubation and withdrawal times

Procedure time	Cap-assisted colonoscopy (min)	Endocuff-assisted colonoscopy (min)	Difference (95% confidence interval)	P value
Cecal intubation time, first	7 (5-10)	6 (4-8)	–1 (–2 to 0)	.01
Cecal intubation time, second	6 (4-7)	4 (3-6)	–2 (–1 to 0)	.005
Withdrawal time, first	8 (6-11)	10 (7-15)	2 (0-3)	.01
Withdrawal time, second	6 (5-7)	6 (5-8)	0 (0-1)	.40
Negative withdrawal time, first	6 (5-8)	6 (6-7)	0 (0-1)	.47
Negative withdrawal time, second	6 (5-7)	5 (4-6)	–1 (–1 to 0)	.07

Values are median (interquartile range) unless otherwise defined.

study.^{16,17,27} This could be because of improved design of EV compared with the original Endocuff with 2 rows of finger-like projections.

One of the disadvantages of EAC in our study was that a small number of procedures were incomplete and EV had to be removed to complete the procedure. Ten of 152 procedures (6.2%) were not completed because of the inability to negotiate a fixed or angulated sigmoid colon or because of discomfort. EV had to be removed to complete the examination. This observation was noted in 4 recent trials of Endocuff, and the cuff removal rate was similar to our study (4%-6.4%).^{21,29-31} The potential reasons for this inability to negotiate is probably secondary

to the increase in the tip diameter of the colonoscope by 1 to 2 mm by addition of EV and possibly more frictional resistance at the colonoscope tip in a narrowed or angulated colon. Conversely, constant interval reciprocating was 100% in CAC, and it appears that the cap design (soft plastic material and slight projection beyond the distal end of the endoscope) does not impede insertion through a fixed or angulated sigmoid colon and may even be advantageous, providing enhanced vision in a narrowed lumen when all air is suctioned by keeping the mucosal folds away from the colonoscope tip.

Overall patient experience was similar in both groups, and most patients (>94%) tolerated the procedures very

well regardless of the device used. With regard to anal discomfort on insertion, patients reported that EAC was slightly more uncomfortable than CAC. When a colonoscopy is performed with the patient under mild, conscious sedation or no sedation, endoscopists should be aware of this issue and apply adequate lubrication and advocate gentle insertion technique.

Ileal intubation was not routinely attempted during this study. Our impression is that EV does not hinder distal terminal ileal intubation. However, deep ileal intubation was rarely possible with EV. Conversely, CAC appears to help passage into the terminal ileal and deep ileal intubation.

The strengths of this study are its tandem, crossover study design, in which the same endoscopist performed both procedures one after another. In addition, all demographic and procedure variables were equivalent between both groups. Almost all previous studies comparing adjunct devices with SC have been performed by very experienced endoscopists. In our study, participating endoscopists were moderately experienced and still in a gastroenterology training program, so results may be more generalizable to average clinical practice.

One previous randomized study of EV versus SC (E-Cap study) where 4 highly experienced colonoscopists performed all procedures did not show any advantage in ADR with EV,³⁰ but the larger ADENOMA randomized trial did show an advantage for EV. In the latter trial, most colonoscopists were very experienced.²¹ However, in our study the procedures were performed by moderately experienced colonoscopists, which may confirm that the benefit of EV is seen both in trainees and experienced colonoscopists.

The study limitations are its single-center design involving only 3 endoscopists, and the endoscopists were not blinded for the device in use. This is a common and a consistent limitation with all endoscopic studies evaluating devices and novel technologies where blinding is not possible.

In conclusion, our study demonstrated that EV surpassed the performance of CAC, significantly reducing the AMRs in the hands of moderately experienced endoscopists. However, the EV did need to be removed in a small minority of technically difficult colonoscopies.

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Abbreviations: ADR, adenoma detection rate; AMR, adenoma miss rate; CAC, cap-assisted colonoscopy; CIT, cecal intubation; CRC, colorectal

cancer; DPC, dynamic position change; EAC, Endocuff-assisted colonoscopy; EV, Endocuff Vision; MAP, mean adenomas per procedure; SC, standard colonoscopy; SSA/P, sessile serrated adenoma/polyp; WT, withdrawal time.

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SUPPLEMENTARY TABLE 1. Comparison of number of dynamic position changes during insertion and withdrawal

Phase of colonoscopy procedure	Cap-assisted colonoscopy	Endocuff-assisted colonoscopy	Difference (95% confidence interval)	P value
Insertion, first	2.3 (.9)	2.0 (.7)	-.3 (-.5 to -.1)	.04
Insertion, second	2.1 (.7)	2.0 (.6)	-.1 (-.3 to .1)	.47
Withdrawal, first	3.3 (.8)	2.4 (.7)	-.9 (-1.1 to -.6)	<.001
Withdrawal, second	3.1 (.8)	2.2 (.6)	-1.0 (-1.2 to -.7)	<.001

Values are mean (standard deviation) unless otherwise defined.

SUPPLEMENTARY TABLE 2. Patient experience of discomfort during tandem colonoscopy

Patient experience	Category	Cap-assisted colonoscopy	Endocuff-assisted colonoscopy	P value
Anal discomfort	Comfortable	67 (85.9)	29 (39.2)	<.001
First procedure	Minimal	8 (10.3)	51 (55.4)	
	Mild	1 (1.3)	4 (5.4)	
	Moderate	2 (2.6)	0 (.0)	
Anal discomfort	Comfortable	66 (89.2)	26 (35.6)	<.001
Second procedure	Minimal	8 (10.8)	44 (60.3)	
	Mild	0 (.0)	2 (2.7)	
	Moderate	0 (.0)	1 (1.4)	
Discomfort score	Comfortable	19 (24.7)	17 (23.3)	.86
First procedure	Minimal	51 (66.2)	52 (71.2)	
	Mild	6 (7.8)	3 (4.1)	
	Moderate	1 (1.3)	1 (1.4)	
Discomfort score	Comfortable	21 (28.4)	13 (18.6)	.17
Second procedure	Minimal	49 (66.2)	52 (74.3)	
	Mild	4 (5.4)	5 (4.1)	
	Moderate	0 (.0)	0 (.0)	

Values are n (%).

Appendix 3

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Colon (C Kahi, Section Editor)

Electronic Imaging in Colonoscopy: Clinical Applications and Future Prospects

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Keywords Electronic chromoendoscopy • NBI • FICE • i-Scan • Diminutive polyps • Optical diagnosis

Opinion statement

Electronic chromoendoscopy (EC) is an equipment-based technology which could be easily activated by push of a button. There are four EC techniques available for use at present: narrow band imaging (NBI), i-Scan, flexible spectral chromoendoscopy and blue laser imaging. Out of the four techniques, NBI has been extensively evaluated for the detection and characterization of dysplasia in colonic polyps and dysplasia associated with inflammatory bowel disease. In this review, we will focus on the new developments and applications of EC.

Introduction

Colorectal cancer (CRC) is one of the commonest causes of significant morbidity and mortality in the western world. It is the second most common cause of cancer-related mortality in Europe and the fourth most common cause worldwide [1]. Sporadic CRC arises from adenomatous polyps in a well described adenoma-carcinoma sequence [2]. Approximately, 15–30 % of CRC arise via serrated pathway from precursor lesions and serrated adenomas [3]. Familial CRC and CRC associated with

inflammatory bowel disease also arise from dysplastic lesions which can be detected at colonoscopy.

Colonoscopy is the most valuable weapon in the fight against CRC. The efficiency of CRC prevention with colonoscopy depends on complete and careful inspection of colonic mucosa for dysplastic lesions and their successful removal before they progress to cancer [4]. Various techniques have been developed to improve the detection

and characterization of dysplastic lesions including chromoendoscopy, electronic chromoendoscopy and autofluorescence [5•, 6•].

Electronic chromoendoscopy (EC) refers to endoscopic imaging technologies which provide detailed contrast enhancement of the mucosal surface and blood vessels. They provide an alternative to conventional chromoendoscopy and improve mucosal visualization of surface and vascular structures through the use of optical filters or software-driven post-image processing [6•, 7]. EC technologies include narrow band imaging (NBI) (Olympus Medical Co., Tokyo, Japan), flexible spectral imaging colour enhancement (FICE) (Fujinon, Fujifilm Co., Saitama, Japan), i-Scan (Pentax Endoscopy, Tokyo, Japan) and blue laser imaging (BLI) (Fujinon, Fujifilm Co., Saitama, Japan).

NBI is an endoscopic optical image enhancement technology. It is based on the penetration properties of light, which is directly proportionate to wavelength. Because most of the NBI light is absorbed by the blood

vessels in the mucosa, the resulting image emphasizes the blood vessels in sharp contrast with the non-vascular structures in the mucosa. FICE is a digital imaging post-processing technique, in which white light endoscopic images from the video processor are altered to display a composite colour-enhanced image in real time. i-Scan (Penatax) is similarly a software-based digital, post-processing image enhancement technology. It provides enhanced images of the mucosal surface and the blood vessels through post-image processing. i-Scan enhances contrast and thereby mucosal surface detail including enhanced mucosal surface texture and sharpened views of surface vessels, thereby improving the visibility of blood vessels [6•].

NBI is the most extensively evaluated EC technique in patients undergoing screening or surveillance colonoscopy.

In this review, we focus on the latest developments in the field of electronic chromoendoscopy during colonoscopy, applications and future directions.

Electronic chromoendoscopy and detection of dysplasia

Adenoma detection

Adenoma detection rate (ADR) is one of the key quality indicators of colonoscopy and has been shown to inversely correlate with post-colonoscopy interval cancers [8].

NBI

NBI is the most extensively evaluated EC modality in terms of adenoma detection. Multiple randomized controlled trials showed there was no significant difference in adenoma detection of NBI when compared to white light endoscopy (WLE). East and colleagues randomized 214 patients to examination with NBI or WLE [9]. They showed there was no significant difference in ADR between NBI and WLE (OR 1.4, 95 % CI 1.52–4.63, $p = 0.26$). However the detection of flat adenomas were significantly better with NBI (CR 1.92, 95 % CI 1.07–3.44, $p = 0.003$) [9]. Similar results were described in the study performed by Ikematsu et al. [10] in a multicentre, tandem study that randomized 813 patients to undergo either NBI followed by WLE or WLE followed by NBI. They detected no significant difference in ADR (42.3 % for NBI and 42.5 % for WLE).

Meta-analyses comparing WLE and NBI for the detection of adenomas are summarized in Table 1 [11–15]. Overall, the superiority of NBI over WLE for adenoma detection is not universal and not convincing. One meta-analysis showed that NBI performed better in detecting flat adenomas (RR 1.96, 95 % CI 1.09–3.52, $p = 0.02$) [11].

A recent study comparing new-generation NBI (Olympus Exera HQ190) and high-definition (HD) WLE in a randomized trial with

Table 1. Meta-analysis comparing NBI and WLE

Author	Year of publication	No. of studies	Total no. of patients	ADR
Jin et al. [11]	2011	08	3049	RR 1.09 (95 % CI 1.00–1.19)
Dinesen et al. [12]	2012	07	2936	RR 1.06 (95 % CI 0.92–1.16)
Nagorni et al. [13]	2012	08	3673	RR 0.94 (95 % CI 0.87–1.02)
Pasha et al. [14]	2012	09	3059	OR 1.01 (95 % CI 0.74–1.37)
Omata et al. [15]	2014	14	5074	RR 1.03 (95 % CI 0.96–1.11)

RR relative ratio, OR odds ratio, CI confidence interval

tandem colonoscopy showed encouraging results for NBI [16••]. ADR were significantly better in the NBI group when compared to WLE (48.3 and 34.4 %, $p=0.01$). Similarly, polyp detection rate was better with NBI (61.1 and 48.3 %, $p=0.02$).

Sessile serrated lesions

These polyps could be easily missed due to the subtle appearance (pale colour, poorly defined edges and the presence of mucus on the surface) [17••]. Therefore, endoscopists need to spend additional time to carefully examine the mucosa for sessile serrated adenomas/polyps (SSA/P) especially in the right colon.

NBI has the potential to improve the detection of subtle lesions. Recently, Rex and colleagues performed a randomized controlled trial involving 804 patients to determine the impact of new-generation NBI (Olympus 190 series) to detect SSA/P [18••]. Although numerically more SSA/P proximal to the sigmoid colon of any size were detected in NBI group when compared to WLE group (204 and 158, $p=0.085$), this was not statistically significant.

FICE

There is limited data available on the use of FICE. Two prospective, randomized, controlled trials that compared FICE with WLE failed to show any improvement in polyp detection or adenoma detection. Ainalai et al. recruited 637 patients into each group [19]. There was no difference in polyp detection (31.9 % with FICE and 27.7 % with WLE, $p=0.10$) or ADR (28 % each, $p=0.95$). The second trial performed by Pohl et al. involving 764 patients did not demonstrate an improvement in adenoma detection with FICE compared to WLE (236 and 271, $p=0.92$) [20]. A randomized, tandem study in average-risk patients undergoing screening colonoscopy compared WLE with either NBI or FICE [21]. Chung et al. recruited 1650 subjects (550 in each group). FICE did not show any increment in ADR when compared with WLE or NBI (25.3 and 24.5 %, $p=0.75$). Similarly, a meta-analysis conducted by Omata and colleagues, comparing FICE/i-Scan showed no benefit over WLE (RR 1.09, 95 % CI 0.97–1.23) [15].

i-Scan

The studies using i-Scan in the detection of adenomas showed mixed results. Hoffmann et al. highlighted a superior ADR with i-Scan when compared to

WLE (38 and 13 %, $p < 0.0001$). The detection rate for flat adenomas was higher with i-Scan compared to WLE (58 and 23 %, $p < 0.0001$) [22]. However, the very low ADR in the white light group in this study may have exaggerated the potential benefit of i-SCAN. Two further prospective, tandem studies showed conflicting results. Once again, Hoffmann et al. showed significantly low adenoma miss rate with i-Scan compared to WLE (30 and 62.5 %, $p < 0.001$) [23] whereas another back to back study demonstrated no significant difference in ADR (36.5 and 31.9 %, $p = 0.54$) and adenoma miss rate (19.3 and 22.9 %, $p = 0.69$) comparing WLE and i-Scan [24]. The largest prospective, randomized trial comparing i-Scan with HD WLE involving 1936 patients showed promising results [25••]. Polyps and adenomas were consistently detected more frequently in the i-Scan cohort; 56 % of the i-Scan group patients had a polyp of any type detected compared to 47 % in the control group ($p = 0.03$). Adenomas were detected more frequently in the i-Scan group compared to the WLE group (33 and 27 %, $p = 0.033$). Significantly, more diminutive adenomas were found in the i-Scan group compared to the control group (40.2 and 28.0 %, $p < 0.01$) [25••].

BLI

To date, there is no published data available on the use of BLI to improve adenoma detection.

In summary, EC especially NBI and i-Scan may improve the detection of diminutive polyps. However, none of the modalities demonstrated consistent improvement in ADR, and, therefore, the routine use of EC is not currently recommended for routine screening or surveillance colonoscopy.

Electronic chromoendoscopy in inflammatory bowel disease

Long-standing history of ulcerative colitis and Crohn's colitis are well recognized risk factors for the development of CRC. The cancer risk increases with extent, duration and degree of inflammation, presence of primary sclerosing cholangitis and family history of CRC [26–28].

Therefore, regular surveillance in IBD population is recommended by all major society guidelines (British Society of Gastroenterologists (BSG), European Crohn's and Colitis Organization (ECCO), European Society of Gastrointestinal Endoscopy (ESGE), American Gastroenterological Association (AGA)) [29–32].

European guidelines (ESGE, ECCO and BSG) recommend the routine use of pancolonoscopic chromoendoscopy with targeted biopsies for neoplasia surveillance in patients with long-standing colitis [29–32]. However, chromoendoscopy technique is unappealing as it prolongs the procedure time in addition to being cumbersome as well as requiring sufficient expertise [33].

EC has the advantage over traditional chromoendoscopy as the image enhancement mode can be activated by push-button technology, and it is cheaper, quicker and more user-friendly.

Two randomized controlled trials compared high-definition (HD) NBI to CE. In a tandem study performed by Pellise et al., patients with long-standing colitis ($n = 60$) were randomized with HD NBI or CE [34]. The study showed no significant difference in dysplasia detection, and although NBI showed a numerically higher miss rate for dysplastic lesions when compared to CE (13.6 vs

31.8 %), this was not statistically significant [34]. A multicentre parallel randomized study involving 108 patients with chronic colitis showed a comparable detection rate for dysplastic lesions (18 with NBI and 26 with CE, $p = 0.385$) [35]. Efthymiou et al. performed a back to back study with HD NBI followed by CE in patients with long-standing colitis (>8 years duration) [36]. Overall, CE detected more lesions than NBI (131 vs 103, $p < 0.001$); however, most of them were non-dysplastic. There was no difference in dysplasia detection—CE detected 23 dysplastic lesions in 11 patients and NBI 20 lesions in 10 patients ($p = 0.18$). Similarly, studies comparing NBI with standard WLE failed to show any improvement in the detection of dysplasia [37, 38].

To date, NBI has failed to show any improvement in the detection of dysplasia in IBD when compared to WLE or CE. There are no published data available using FICE, i-Scan and BLI in colitis surveillance.

In summary, the current evidence does not support the use of EC in surveillance in IBD at present.

Polyp characterization and optical diagnosis

The current practice mandates that all small polyps detected during colonoscopy should be resected and sent for histopathological assessment to determine the histopathological type (adenoma, hyperplastic or more recently serrated lesions), as colonoscopic surveillance intervals are influenced by the number, size and histological features of polyps (i.e. adenoma, presence of villous features and high-grade dysplasia) [39, 40]. The majority of polyps detected at colonoscopy are diminutive (<5 mm) and rarely harbour cancer or high-risk features such as high-grade dysplasia or villous component [41, 42, 43••].

As diminutive polyps are of such limited significance, being able to diagnose adenomas in vivo would allow for them to be resected and discarded, saving the costs associated with histopathology. Furthermore, diagnosing distal hyperplastic polyps in vivo would allow for these to be left in situ (diagnose and disregard) reducing the risks associated with polypectomy [43••]. Estimates suggest that by implementing resect and discard policy savings of \$33 million to \$1 billion could be made annually in the USA alone [44]. Recent generation of high-definition instruments with virtual or electronic chromoendoscopy has enabled endoscopists to attempt to predict the histological type of polyps in vivo.

NBI

Majority of the studies assessed NBI, a blue light optical imaging modality which enhances the mucosal architecture, especially vasculature. Vascular density and pattern differ between neoplastic (adenoma) and non-neoplastic (hyperplastic) polyps, allowing an endoscopist to use NBI to differentiate between the two (Fig. 1) [45]. A group of international experts have developed and validated a system to characterize small colonic polyps: the NBI International Colorectal Endoscopic (NICE) Classification (Table 2) [46]. This classification uses mucosal colour, vessel and surface pattern to differentiate between hyperplastic polyps and adenoma (Table 2). It is applicable for non-magnified NBI imaging. Authors made a diagnostic prediction with high confidence in 75 % of the 236 polyps (82 % in adenomas and 64 % in hyperplastic). These diagnoses achieved accuracy of 88 %, sensitivity of 98 % and negative predictive

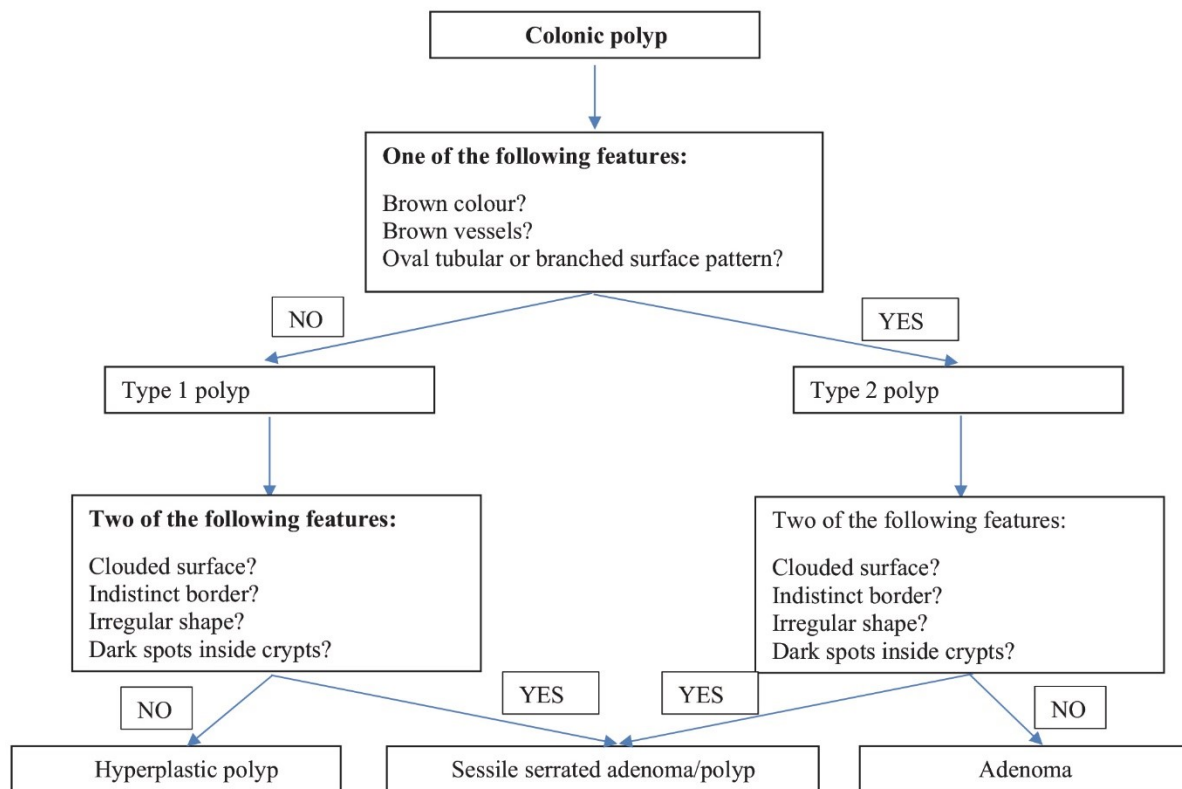


Fig. 1. NBI images of polyps. Clockwise: NBI images of hyperplastic polyp, adenoma, adenoma, SSA/P and SSA/P.

value of 95 % for diminutive polyps [46]. A meta-analysis by Wanders and colleagues evaluated real-time optical diagnosis by NBI and showed an overall sensitivity 91 % (95 % CI 88.6–93.0), specificity 85.6 % (81.3–89.0) and real-time negative predictive value 82.5 % (75.4–87.9) [47]. However, most of the studies in the meta-analysis were carried out by expert endoscopists in academic centres [47]. Ladabaum and colleagues prospectively evaluated real-time optical diagnosis of polyps with NBI by community-based gastroenterologists [48]. This study showed inferior results when compared to the academic centres with sensitivity, specificity and negative predictive values of 85, 78 and 91 %,

Table 2. NICE classification

Colour	Same or lighter than background	Browner relative to background
Vessels	None or isolated lacy vessels coursing across the lesion	
Surface pattern	Dark or white spots of uniform size or homogenous absence of pattern	Oval, tubular or branched white structures surrounded by brown vessels
Most likely pathology	Hyperplastic	Adenoma

Adapted from Hewett DG, Kaltenbac T, Sano Y, et al. Validation of a simple system for endoscopic diagnosis of small colorectal polyps using NBI. *Gastroenterology* 2012;143:599–607.e1; with permission

respectively. New NBI system with near focus might offer a solution for this discrepancy as near-focus image may provide a more detailed view of the surface architecture. Singh et al. assessed 149 polyps using Olympus 190 series Exera III NBI system with dual focus (DF) capabilities [49]. The overall accuracy of NBI-DF when compared to final histopathology was 97 %. In addition, post-polypectomy surveillance interval when based on optical diagnosis was accurate in 97 % of cases with high negative predictive value (100 %) for diminutive rectosigmoid polyps.

SSA/P

It is often difficult if not impossible to differentiate hyperplastic polyps (HP) from SSA/P on white light endoscopic examination. Yamada et al. performed a retrospective image evaluation study in which 242 NBI lesions were evaluated by 2 experienced endoscopists [50●●]. Multivariate analysis demonstrated that the presence of Dilated and branching vessels (DBV) on the surface had a 2.3-fold odds ratio (95 % CI 0.96–5.69) among SSA/P compared to HPs. When DBV, proximal location and polyp size >10 mm were combined, the positive predictive value reached 92 % for SSA/P making it promising for the optical diagnosis of serrated lesions. Recently, IJspeert and colleagues developed a new classification system for in vivo differentiation of adenomas, HPs and SSA/P; the Workgroup serrated polypS and Polyposis (WASP) classification (Fig. 2) [51●●].

FICE

Teixeira and colleagues proposed an endoscopic classification of the superficial capillary-vessel pattern of colorectal lesions to differentiate neoplastic polyps from non-neoplastic polyps: types 1 and 2 are hyperplastic polyps, types 3 and 4 are adenomas and type 5 capillary pattern indicates invasive cancer [52]. The authors analysed 309 colorectal lesions using the Teixeira capillary-vessel pattern classification and found 99.2 % sensitivity and 94.9 % specificity for neoplastic lesions [52].

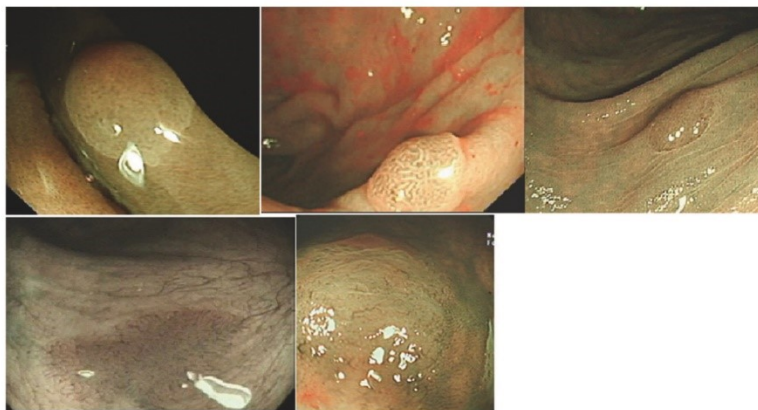


Fig. 2. WASP classification. Adapted from IJspeert JE, Bastiaansen BA, van Leerdam ME, et al. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. Gut 2015;0:1–8; with permission.

Large prospective UK series by Longcroft-Wheaton et al. compared FICE with WLE and found that FICE improved the accuracy of in vivo diagnosis of adenoma from 75 to 88 % ($p < 0.001$) [53]. When using FICE, endoscopists predicted post-polypectomy surveillance interval with accuracy of 97 %. The previously mentioned meta-analysis by Wanders et al. examined 14 studies which used FICE to distinguish neoplastic polyps from non-neoplastic polyps in vivo during screening colonoscopies [47]. FICE showed a sensitivity of 91.8 % and negative predictive value of 83.7 %.

i-Scan

A recent meta-analysis of 11 studies using i-Scan to differentiate neoplastic polyps from non-neoplastic polyps, which included 925 patients with 2312 polyps, demonstrated a sensitivity of 91.5 % and specificity of 92.1 % [54].

BLI

Blue laser imaging (BLI) by Fujinon LASEREO system allows for narrow band observation. The BLI light is useful for acquiring mucosal surface information such as vascular and surface patterns (Fig. 3). Yoshida et al. retrospectively examined 314 colorectal polyp images [55]. The overall diagnostic accuracy of BLI without magnification for differentiating between neoplastic and non-neoplastic polyps (<10 mm) was 95.2 %, which was greater than that of WLE (83.2 %).

In summary, EC is a promising imaging technology to make an accurate optical diagnosis in vivo. NBI has been extensively evaluated and is highly accurate in expert hands in predicting the histopathology of small polyps. It is a user-friendly and easy to apply technique with a push of a button. FICE and i-Scan showed encouraging results. BLI technique needs to be explored further in randomized controlled trials.

Implementation of optical diagnosis

The initial clinical studies suggested that optical diagnosis for diminutive colorectal polyps could be feasible and safe in routine clinical practice. However, recent reports suggest that optical diagnosis performed by non-academic gastroenterologists could not reproduce similar results. Therefore, certain key steps should be followed before translating optical diagnosis into the community practice.

Consequently, the American Society of Gastrointestinal Endoscopy (ASGE) developed a Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement for in vivo endoscopic assessment of diminutive polyps [56•]. Furthermore, a recent update on 'implementation of optical diagnosis of colorectal polyps' raised the issues of training, competency assessment and

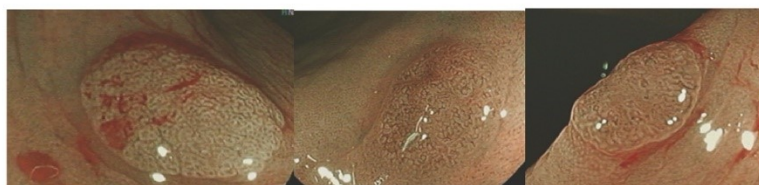


Fig. 3. BLI images of polyps. Clockwise: BLI images of hyperplastic polyp, adenoma and adenoma.

documentation before optical diagnosis could be implemented into routine clinical practice [57].

Training and competency assessment

The knowledge and skills required to perform optical diagnosis can be learned by people with varying experiences in colonoscopy. Ignjatovic et al. from St Mark's Hospital used a still image-based teaching module to differentiate between adenomas and hyperplastic polyps [58]. They showed improved accuracy and specificity of optical diagnosis for all group of participants which included novices, trainees and experienced colonoscopists after a short training module ($k=0.56$, 0.70 and 0.54 , respectively). Recently, WASP classification showed some promising results in differentiating HPs from SSA/P [51••]. In a still image evaluation setting, the introduction of the WASP classification significantly improved the accuracy of optical diagnosis overall and proved to be sustainable after 6 months. Overall, the accuracy of optical diagnosis improved from 63 % before training to 79 % after training ($p<0.001$) and remained at 76 % after 6 months. This study highlighted the importance of continued training and re-assessment of individuals who perform optical diagnosis to maintain the threshold. The fact ex vivo training does not necessarily translate into actual clinical practice was highlighted by the study by Ladabaum and colleagues [48]. In an evaluation of real-time optical diagnosis with NBI, only 25 % of gastroenterologists assessed polyps with ≥ 90 % accuracy while more than 83 % of gastroenterologists performed with >90 % accuracy ex vivo.

These findings suggest that in vivo training with feedback and assessment is needed before non-academic gastroenterologists are certified to perform optical diagnosis in routine clinical practice.

Documentation

High-quality image of the polyp assessed by optical modality should be taken for quality assurance and medicolegal purposes. The question of whether high-quality video clips are necessary for documentation remains to be answered.

Conclusion

The routine use of EC is becoming more popular among the western endoscopists as an alternative to traditional chromoendoscopy due to its wider availability and user-friendly nature. Although there is uncertainty whether NBI improves overall adenoma detection, there are trends that suggest that it may improve the detection of diminutive polyps and sessile serrated polyps. Furthermore, NBI is superior in characterizing polyps especially sessile serrated adenomas when compared to white light. Recent studies showed promising results for i-Scan as well. There is an unprecedented focus on real-time prediction of histology using EC. This ability would allow the endoscopists to predict the surveillance intervals immediately after the colonoscopic examination and could potentially lead to significant cost savings to the health care system. However, the implementation of optical diagnosis in clinical practice needs to be agreed by the relevant gastroenterological societies. Robust and rigorous

training, accreditation and quality assurance aspects need to be agreed and validated.

Compliance with Ethical Standards

Conflict of Interest

Rajaratnam Rameshshanker declares no conflict of interest. Ana Wilson reports personal fees from Cosmo Pharmaceuticals, outside the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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This article highlights the importance of regular surveillance and subsequent management of dysplasia associated with inflammatory bowel disease.

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OPINION

Number of significant polyps detected per six-minute withdrawal time at colonoscopy (SP6): a new measure of colonoscopy efficiency and quality

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INTRODUCTION

Quality assessment of the colon consists of detailed, systematic and meticulous inspection of the entire colonic mucosa. A thorough and careful mucosal inspection is essential to prevent colorectal cancer (CRC) and cancer-related mortality.¹ The detection and resection of precancerous polyps is the primary goal of screening colonoscopy. Recently, there has been a focus on quality and safety of colonoscopy. Worldwide, the demand for colonoscopy is increasing, and with a limited workforce, efficient working is of paramount importance.²

Quest for a colonoscopy efficiency marker

We performed an extensive search in the literature for the definition of colonoscopic efficiency (CE); however, no clear definition was found. We propose the following working definition as 'the ability to detect clinically significant pathologies within acceptable time limits without compromising the quality or safety of the examination'.

CE is augmented by the following factors: optimal bowel preparation, technical ease of the procedure, technique of the endoscopist, high-definition and high-quality video imaging, and uninterrupted panoramic view of mucosal surface.

Although mucosal views may be improved with dynamic position changes and routine retroflexion in the rectum, these manoeuvres may not be effective in narrower colonic segments and flexures.³

Recent technological developments in the field of colonoscopy such as

wide-angle view colonoscopes and disposable distal attachments (Endocuff Vision, transparent cap and Endorings) helped to improve the lateral and backward view of the mucosal folds.^{4–9}

These advancements demonstrated an improvement in the quality and performance of the procedure. However, none of the studies explored the impact on CE of the technologies. We aimed to assess the performance of a new marker of colonoscopic efficiency. We propose SP6 (number of significant polyps detected per 6 min withdrawal time during colonoscopy) as the novel efficiency marker.

METHODOLOGY

We performed a retrospective evaluation of prospectively collected data from our endoscopy database to assess the value of SP6 to compare different detection interventions (Endocuff-assisted colonoscopy (EAC) and standard colonoscopy (SC)). SP6 was calculated using the following simple formula:

$$SP6 = \frac{\text{Number of adenomas and sessile serrated polyps}}{\text{Total withdrawal time}} \times 6$$

For consecutive screening colonoscopies performed between October 2014 and September 2016 at our institution, patient demographic data and procedural data were retrieved from our endoscopy database. We included colonoscopies performed by seven experienced, UK bowel cancer screening programme accredited endoscopists with excellent performance indicators (caecal intubation rate >95%, adenoma detection rate



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Table 1 Polyp and procedural characteristics

	Endocuff-assisted colonoscopy	Standard colonoscopy	P value
No of patients	256	238	NS
Caecal intubation rate	99.6%	98.9%	NS
Caecal intubation time (mean±SD)	5.9±3.0	7.1±3.85	0.39
Withdrawal time (mean±SD)	12.9±4.5	11.8±5.33	0.72
No of polyps	343	159	0.001
No of adenomas	285	112	0.0005
No of SSA/Ps	28	20	1.0
ADR	84.4%	58.4%	0.004
SP6 (adenomas/SSA/P)	1.18	0.62	0.0004
MPP	1.34	0.66	0.001

ADR, adenoma detection rate; MPP, mean number of polyps detected per patient; NS, not significant; SP6, number of significant polyps detected per 6 min withdrawal time during colonoscopy; SSA, sessile serrated adenoma; SSP, sessile serrated polyp.

(ADR) >50%). Every endoscopist performed at least 5000 colonoscopies in clinical practice. All patients were either faecal occult blood test (FOBT) positive or undergoing surveillance colonoscopy within the programme.

RESULTS

A total of 494 patients (age range, 60–75 years) underwent surveillance colonoscopy during this period. Colonoscopy was performed for the following indications: screening following a positive FOBT (54%) and surveillance following previous polypectomy (46%). **Table 1** summarises the procedural and polyp characteristics. There were no significant differences in the caecal intubation rate ($p=0.99$), caecal intubation time ($p=0.39$) or withdrawal time (WT) ($p=0.72$) between EAC and SC. However, total number of polyps and adenomas detected and resected were significantly higher in EAC than SC ($p=0.005$ and $p=0.0001$, respectively). **Table 2** highlights the fact that there were no significant differences in WT between EAC and SC, when no polyps were detected during the procedure.

DISCUSSION

There are several quality indicators in use to assess the quality of colonoscopic examinations including caecal intubation rate, WT more than 6 min and ADR.^{10–13} ADR has been extensively studied and considered as

Table 2 Correlation of withdrawal time (WT) when no polyps were detected during colonoscopic examination

	Endocuff-assisted colonoscopy	Standard colonoscopy	P value
No of patients	27	61	<0.01
WT (mean±SD)	8.59±2.28	6.24±2.89	0.089

the most important performance marker of colonoscopy.^{12–14} It exhibits many advantages as a quality indicator. It is easy to calculate, understand and apply in clinical practice and in trials.¹⁵ Moreover, large studies have shown that ADR correlates well with interval CRC rate and mortality.^{16,17} However, there are fundamental problems with using ADR alone as a marker of colonoscopic quality and performance. First, the ADR does not take into account detection of sessile serrated adenomas/polyps (SSA/P), thought to be the precursor lesions of 15%–20% of all CRCs.¹⁸ Second, it has the potential for the colonoscopist to ‘switch off’ after one adenoma has been detected (*‘one and done phenomenon’*) and does not reward the detection of multiple polyps in the same patient.¹⁹ Third, it does not measure how time-efficiently the endoscopist detects and removes polyps. This final point is of particular importance given the increasing volume of colonoscopy and the need to conduct colonoscopy lists in a timely and effective manner. Therefore, ADR cannot be used to assess the efficiency of an endoscopist, technique or colonoscopy aid.

We suggest a new and simple metric, SP6, as a quality and efficiency marker. SP6 takes into account detection and removal of all potential pre-cancerous lesions (adenomas and SSA/P) and measures how efficiently those polyps are detected and removed. SP6 is easy to calculate, user friendly and a highly reproducible marker.

$$SP6 = \frac{\text{Number of adenomas and SSA/P}}{\text{Total withdrawal time}} \times 6$$

In this study, we have demonstrated that SP6 could be used to compare the performance of novel interventions or techniques. For example, our data showed that EAC significantly improves colonoscopy performance and overall efficiency of the procedure when compared with SC.

We have to bear in mind that when we interpret the performance of any novel devices or interventions, the quality of the procedure should not be compromised in order to improve the efficiency. Both quality and efficiency of the procedure should be enhanced in parallel. European Society of Gastrointestinal Endoscopy (ESGE) and American Society of Gastrointestinal Endoscopy mandated minimum withdrawal time of 6 min for diagnostic examinations. It is clearly mentioned in the guidelines that this figure only applies to examinations in which no polyps are found as detection and resection of polyps increases duration of the procedure.^{20,21} **Table 2** shows that when no polypectomies were performed, EAC (intervention) did not compromise the recommended withdrawal time of 6 min which highlights that the add-on device does not compromise the quality when improving the overall efficiency of the procedure.

Finally, the quality indicators such as WT and ADR could be gamed, where the target measure is achieved but without reflecting the high-quality examination.¹⁹

The chances of potential gaming for SP6 is minimal as it incorporates time as an important assessment factor.

Conversely, SP6 could be gamed during the procedure. This could occur when an endoscopist attempts to remove larger polyps (>2cm) and be tempted to complete the procedure within a given time slot. This would result in incomplete polypectomy and recurrence. In order to minimise this effect, we did not include procedures where large (>2cm) polypectomies were performed. One could argue that polyps of difficult nature (ie, peri-appendiceal location, recurrent/fibrotic polyps, polyps located within a diverticular segment) could take a longer time or highly advanced therapeutic modality to resect and they could adversely affect SP6. During these difficult situations, SP6 could be falsely low. However, this could be a positive argument for SP6 as it would clearly identify whether adjunct devices or interventions are superior in dealing with difficult polyps. In other words, SP6 marker could be used to compare the superiority of a device/intervention against each other.

In our cohort, we did not include any of the procedures which demands an additional session or advanced therapeutic modality such as endoscopic submucosal dissection, full-thickness resection or laparoscopy-assisted colonic resection as it may affect the SP6. Finally, SP6 is a modifiable marker, if the recommended WT is changed in the future. For example, ESGE promotes an optimal WT of 10 min and the marker could evolve as SP10.

CONCLUSION

Our proposed efficiency marker SP6 may act as a meaningful new metric to demonstrate high-quality and efficient examinations. SP6 could be used to compare the efficiency of endoscopists' performance and novel endoscopic interventions or devices to aid the procedure. This new metric needs to be validated in randomised controlled trials prior to the implementation. It appears to be promising and perhaps more relevant to a modern colonoscopy practice.

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