Multicentre Randomized Controlled Trial Comparing Standard and High Resolution Optical Technologies in Colorectal Cancer Screening

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Abstract

Background and Objectives: The UK bowel cancer screening program (BCSP) has been established for the early detection of colorectal cancer offering colonoscopy to patients screened positive by faecal occult blood tests. In this multi-site, prospective, randomised controlled trial, we aimed to compare the performance of standard definition Olympus Lucera (SD-OL) with Scope Guide and the high definition Pentax HiLine (HD-PHL).

Patients and Methods: Subjects undergoing a colonoscopy as part of the UK National BCSP at four UK sites were randomised to an endoscopy list run using either SD-OL or HD-PHL. Primary endpoints were polyp and adenoma detection rate (PDR and ADR, respectively) as well as polyp size, morphology and histology characteristics.

Results: 262 subjects (168 males, mean age 66.3±4.3 years) were colonoscoped (133 patients with HD-PHL while 129 with SD-OL). PDR and ADR were comparable within the two optical systems. The HD-PHL group resulted in a PDR 55.6% and ADR 43.6%; the SD-OL group had PDR 56.6% and ADR 45.7%. HD-PHL was significantly superior to SD-OL in detection of flat adenomas (18.6% versus 5.2%, $p<0.001$), but not detection of pedunculated or sessile polyps. Patient comfort, use of sedation and endoscopist perception of procedural difficulty, resulted similar despite the use of Scope Guide with SD-OL.

Conclusion: PDR and ADR were not significantly different between devices. The high-resolution colonoscopy system HD-PHL may improve polyp detection as compared to standard resolution technology in detecting flat adenomas. This advantage may have clinically significant implications for missed lesion rates and post-colonoscopy interval colorectal cancer rates.

Keywords: polyp detection rate, bowel cancer screening, Olympus Lucera, Pentax HiLine, colonoscopy

Short Summary Box

What is already known about this subject?
Standard Definition Olympus-Lucera and High Definition PentaxHiLine are two frequently used high-quality colonoscopy technologies in the UK Bowel Cancer Screening Program. Despite same principles of video endoscopy, diagnostic yield or patient comfort vary with the instrument's individual characteristics.

What are the new findings?
Polyp and adenoma detection rate were comparable within the two optical systems. In a subgroup analysis, High Definition PentaxHiLine was significantly superior to Standard Definition Olympus-Lucera in the detection of flat adenomas.
Patient comfort, use of sedation and endoscopist perception of procedural difficulty, resulted similar despite the use of Scope Guide with Standard Definition Olympus-Lucera.

How might it impact on clinical practice in the foreseeable future?
A higher flat polyp detection rate is likely to have a significant impact on the detection of early cancers or high-grade lesions, as well as the prevention of colorectal cancer and decreased rate of missed lesions.

Introduction

About one in twenty people in the UK will develop colorectal cancer during their lifetime. It is the third most common cancer in the UK, and the second leading cause of cancer deaths, with over 16,000 people dying from this condition each year.[1, 2, 3]

Regular bowel cancer screening has been shown to reduce the risk of dying from bowel cancer by sixteen per cent.[4] Since 2006, the UK has rolled out a national screening programmed for all subjects offering a home test kit for faecal occult blood every two years from 60 to 75 years of age. Patients aged 75 years or over can self-refer. A positive result will lead to an invitation to a colonoscopy that is performed in a bowel cancer screening (BCS) accredited centre by an accredited endoscopist.[5, 6]

Colonoscopy is the gold standard diagnostic tool for detection of colorectal cancer and adenomatous polyps. However, the miss rates for these two pathologies, although low remains a concern. A high quality examination will increase the detection rate of neoplastic lesions in the colon. Hence, the technology involved in colonoscopy has evolved greatly over the past few years and continues to change and adapt endoscopists' needs, providing the tools for fast, precise and safe examinations of the colon.[7, 8, 9, 10, 11, 12]

The three major manufacturers (Olympus, Fujinon, and Pentax) have product lines with similar characteristics. Each provides detailed colour views of the gastrointestinal mucosa through a wide-angle lens. The depth of view ranges from 5mm to 100mm, with nearly 30-fold magnification of the mucosa.

High quality colonoscopy performance also depends on the operator associated quality measures or skills of the endoscopist and can vary significantly. To measure these operator dependant skills, the UK Joint Advisory Group on Gastrointestinal Endoscopy outlined key performance indicators to ensure minimum standards. These include caecum intubation rate above 95% and adenoma detection rate at least 15% in women and at least 25% in men. Olympus (Olympus Europa, GmbH, Hamburg, Germany) and Pentax (Pentax Europe GmbH, Lifecare, Hamburg, Germany) are two frequently used colonoscopy technologies in the UK. Although both use the same principle of video endoscopy, each type of instrument has individual characteristics that allows the endoscopist optimal maneuverability and procedural precision and ultimately a better diagnostic yield with optimal patient comfort.

The Olympus Lucera series scopes have a black and white chip with resolution of approximately 300,000 pixels. It also has a *ScopeGuide* system providing a real-time 3D representation of the shape and position of the endoscope inside the body to minimize patient discomfort during the procedure. This system has been available since 2002 and is currently in wide use for bowel cancer screening colonoscopy.[13, 14, 15, 16]

Several studies have demonstrated the potential advantage of utilising additional optical technologies to improve polyp detection, such as narrow band imaging (NBI) in Olympus and i-scan in Pentax scopes, however results are still conflicting.[13, 14, 15, 16]

The new Pentax HiLine colonoscopes have been available since 2009.[17] They use a colour chip system and have 1.2 Megapixel resolution. The quality of the final endoscopy image viewed on the screen is dependent upon all the components in the system, including the charge coupled device chip within the scope, the processor, the cables and the screen. Charge coupled device chips in the newer 'high resolution' scopes contain more pixels and have increased by an order of magnitude from 100,000 pixels in the older standard definition scopes to 1.3 million pixels in the latest scopes.[18] The current displays are 'high definition' displaying 1080 lines and thereby further improving image quality.

For the purposes of this paper, we use high resolution to describe the overall quality of the image, but also the density of pixels in the endoscope microchip whereas high resolution (HD) to describe only the quality of the screen image measured by the density of lines.

The principal aim of the BCS programme (BCSP) in the UK is to reduce the mortality from colorectal cancer by the early detection of cancerous or pre-cancerous lesions. The accuracy of colonoscopy in order to identify these lesions is vital to the success of the program. Factors important in the optimization of the test include bowel preparation, operator skill, withdrawal time and image quality.[8, 13, 14, 19, 20] Flat and depressed polyps are more likely to contain high-grade dysplasia or invasive cancer than polypoid lesions, but are less easily identified and therefore are more likely to be missed on colonoscopy.[21, 22] If the Pentax HiLine system improves the polyp detection rate and therefore early cancers, there is likely to be a significant impact on the prevention of colorectal cancer. Hence, our aim was to perform a prospective randomised controlled trial to directly compare standard resolution (SD) Olympus Lucera (OL) and high resolution (HD) Pentax HiLine (PHL) colonoscopy systems at multiple sites where the National BCSP is being undertaken (BCSP England and Bowel Screening Wales with the same accreditation and quality standards).

Methods

Patients and Study Design

All patients with a testing positive on a faecal occult blood test and as part of the screening program scheduled to undergo a first (index) colonoscopy as part of the National BCS program were invited to participate in this prospective multi-site randomised study conducted at University College Hospital (London), University Hospital Llandough (Cardiff), Bradford Hospital (Bradford) and Addenbrooke's Hospital (Cambridge). At the time of the study at University College Hospital there were five dedicated endoscopy lists per week as part of the BCS program. There were four dedicated screening lists at Addenbrooke's Hospital and three at University Hospital Llandough and Bradford Hospital. Every potential participant was consecutively allocated to the next available slot during the BCS pre-assessment pathway. Each study site had both Olympus Lucera and Pentax HiLine colonoscopes available. The available slots were in either an Olympus Lucera or Pentax HiLine system list. The person performing allocation was not aware of the system in place for that specific list in order to minimise selection bias. For operational reasons, the entire endoscopy list was run with a single type of endoscope. Therefore, randomisation was on an endoscopy list basis rather than an individual patient basis and was stratified by the endoscopist (list/block randomization). This *passive* randomisation ensured balance to operators and approximately equal numbers in each arm.

Standard of care is that BCS specialist nurses review each patient in a dedicated BCS pre-assessment clinic or by phone, before booking a colonoscopy in a dedicated BCS endoscopy list. A copy of the patient invitation letter and study information leaflet was given to the patient during the visit or sent by post. The endoscopist obtained participants' informed consent prior to the procedure date. We recorded procedure related parameters related to quality assurance and findings at all colonoscopy procedures in the study. Exclusions to recruitment included contraindications to undergoing a colonoscopy and follow up (surveillance) patients.

Endoscopists

Joint Advisory Group certified endoscopists who had satisfied the training requirements to carry out colorectal cancer screening, performed each procedure at the trial sites on a designated BCS endoscopy list.[8, 9, 11, 20, 23, 24] All endoscopists were familiar

with both endoscopic systems used in this trial. Endoscopist difficulty perception was scored based on a three point scoring system (easy-average-difficult), modified from established difficult colonoscopy prediction models.[25]

Scope Settings

The starting settings for colonoscopy were set as follows:
Standard Resolution Olympus Lucera System (SD-OL): White balance colonoscope (CF 260 series), choose enhancement level 2, NBI was used at the discretion of the endoscopist but this was recorded. Use of scope guide was allowed and recorded at the endoscopist's discretion.
High Resolution Pentax HiLine System (HD-PHL): White balance colonoscope, choose i-scan setting off. I-scan 1 was used during withdrawal from the caecum and I-scan 2 & 3 were used at the discretion of the endoscopist but this was recorded.
The optional magnification/contrast tools for both systems (NBI and i-Scan) were defined as magnification add on.

Outcome Measures

The primary outcomes were total polyp detection rate (PDR) and adenoma detection rate (ADR) with sub-analysis for identification of flat adenomas, depending on the use of magnification or contrast tools.
Secondary outcomes were caecal intubation time, caecal intubation rate, total procedure time, withdrawal time, patient comfort scores, sedation used (type and dose), polyp retrieval rate, immediate/ late complications, endoscopists' comments on procedural difficulty.
With regards to polyps' characteristics the following parameters were recorded: localization (site), morphology as described in the PARIS classification (pedunculated, sessile, or flat, maximum height of polyp as assessed by the endoscopist in comparison to the size of standard biopsy forceps); the pathologist also recorded the diameter and depth of the polyp received for analysis.
All data were collected and compared between the two colonoscopy systems. Patients' characteristics included age, sex, presence of diverticular disease, previous abdominal surgery and efficacy of bowel preparation.

Sample Size

For each system, we quantified the proportion of patients with detected adenomas. A sample size of 340 patients was calculated to detect a difference in proportions of 15% based on the previous in service evaluation and standard endoscopic performance as statistically significant using a chi-squared test with 5% statistical significance and 80% power. This was based on a previous retrospective analysis at University College Hospital comparing the two colonoscopy systems, where there were statistically significant differences for a single operator in 50 procedures in favour of PHL.[26]

Statistical Analysis

A chi-squared test was used to perform the primary analysis. For continuous outcomes a t-test or Mann-Whitney test was used. Primary and secondary outcomes were summarised by proportions and means with standard deviations. Two-way analysis of variance (or regression) was used to investigate differences between centres and operators with respect to the secondary outcomes.

Ethics

The study was approved by the National Research Ethics Service Committee London Central, REC reference number 11/LO/1712. The trial has been registered with

ISRCTN Registry, number ISRCTN64724266. CONSORT guidelines were followed during the design of this study.

Results

Descriptives

262 patients were recruited from May 2012 to August 2013 in the three participating BCS centres. 107 patients were enrolled at University College Hospital [51 (47.7%) with SD and 56 (52.3%) with HD Systems], 90 patients at University Hospital Llandough [48 (53.3%) with SD and 42 (46.7%) with HD Systems], 19 patients at Addenbrooke's Hospital [5 (26.3%) with SD and 14 (73.7%) with HD Systems] and 46 patients at Bradford Hospital [24 (52.2%) with SD and 22 (47.8) with HD Systems] (Figure 1). In total, in the HD group, 133 patients were enrolled, 84 males, age 66.1 ± 4.1 years, while 129 subjects were enrolled in the SD group, 84 males, mean age 66.3 ± 4.3. Procedures were performed by six endoscopists who used both optical systems. Each endoscopist performed a mean of 36 ± 21 procedures (range 19-71). There were no significant differences between the SD and HD groups in terms of demographics and pre-endoscopy expected procedural difficulties such as diverticular disease and previous abdominal surgery. Diverticular disease was present in 36.1% (48/133) patients in the HD group and 42.6% (55/129) of the SD group. In the HD system group 7.5% (10/133) of subjects underwent previous abdominal surgery compared to 7% (9/129) in the SD system group. Bowel preparation was good in 55.6% (74/133) and 57.4% (74/129) or adequate in 38.3% (51/133) and 38% (49/129) in the HD and SD groups, respectively, with the majority of patients prepared with Citramag or Kleanprep. Data are summarised in Table 1.

Figure 1. Participant flow chart.

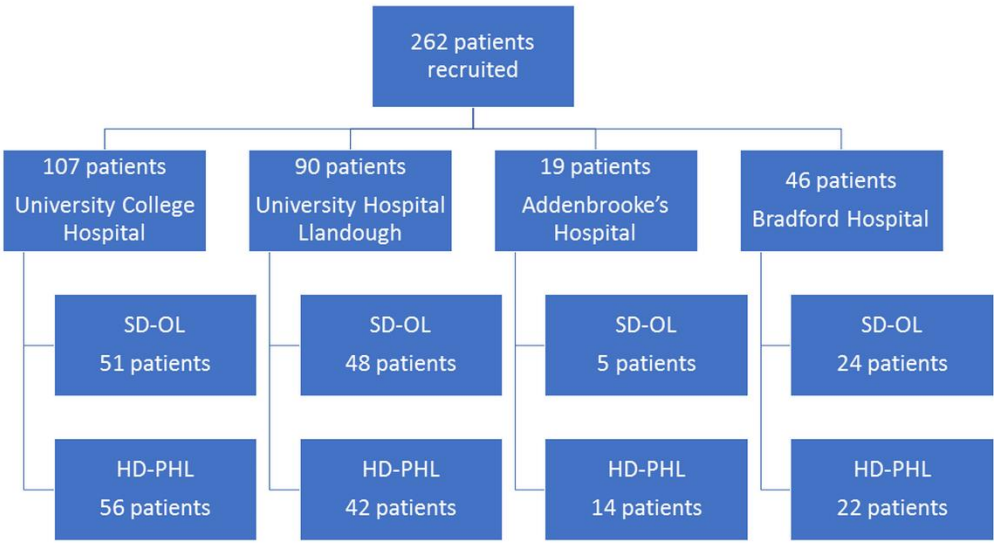

Table 1. High Definition PentaxHiLine (HD) vs Standard Definition Olympus-Lucera (SD) technologies: demographics, Polyp Detection Rate (PDR), Adenoma Detection Rate (ADR) and procedural characteristics.

		patients (n=262)				
		HD (n=133)		SD (n=129)		p-value
Age	*(years, mean±SD)*	66.10± 4.07		66.30± 4.30		
		n	**%**	**n**	**%**	
Gender	*Female*	49	36.8%	45	34.9%	0.80
	Male	84	63.2%	84	65.1%	
PDR	*no*	59	44.4%	56	43.4%	0.90
	yes	74	55.6%	73	56.6%	
ADR	*no*	66	49.6%	65	50.4%	0.45
	yes	58	43.6%	59	45.7%	
	n/a	9	6.8%	5	3.9%	
Diverticular disease	*no*	85	63.9%	74	57.4%	0.31
	yes	48	36.1%	55	42.6%	
Abdominal Surgery	*no*	123	92.5%	120	93.0%	0.91
	yes	10	7.5%	9	7.0%	
Bowel preparation quality	*poor*	8	6.0%	6	4.7%	0.26
	satisfactory	51	38.3%	49	38.0%	
	good	74	55.6%	74	57.4%	
Bowel preparation type	*Citramag*	67	50.4%	55	42.6%	0.31
	Kleanprep	25	18.8%	23	17.8%	
	Other	41	30.8%	51	39.5%	
Retroverted view	*no*	3	2.3%	3	2.3%	0.83
	yes	76	57.1%	69	53.5%	
	n/a	54	40.6%	57	44.2%	
Image or Contrast Enhancement	*no*	102	76.7%	113	87.6%	0.02
	yes	31	23.3%	16	12.4%	
Procedural difficulty	*1*	16	12.0%	10	7.8%	0.71
	2	64	48.1%	64	49.6%	
	3	13	9.8%	13	10.1%	
	n/a	40	30.1%	42	32.6%	
Patient Comfort score	*1*	85	63.9%	86	66.7%	0.23
	2	34	25.6%	22	17.1%	
	3	14	10.5%	18	14.0%	
	4	0	0.0%	3	2.3%	
Sedation used (mean ±SD)	*Midazolam (mg)*	1.44±1.05		1.42±0.83		0.86
	Fentanyl (µg)	47.2±31.3		45.5±27.2		0.64
	Buscopan (mg)	11.13±9.43		10.74±9.98		0.18
Total procedure time (min)		25.49±12.53		26.65±12.62		0.46
Caecal intubation time (min)		10.36±5.47		11.04±6.49		0.36
Withdrawal time (min)		16.54±8.12		17.58±8.43		0.36

n/a, not applicable

Primary Endpoint

A total of 147 patients were diagnosed with at least one polyp. In the HD group, 55.6% (74/133) of patients had at least one polyp (PDR) at colonoscopy while 43.6% (58/133) were adenomas (ADR). In the SD group, PDR was 56.6% (73/129) while ADR was 45.7% (59/129), showing comparable performance of the two optical systems (Table 1). A total of 347 polyps were found, 194 by HD and 153 by SD. Detection stratified for polyps' histology, size or location in the bowel showed similar results. However when data were analysed by morphology of the polyp, HD was significantly superior to SD in the detection of flat polyps [18.6% (36/194) *vs* 5.2% (8/153), p<0.001] and flat adenomas [11.3% (22/194) *vs* 2.6% (4/153), p=0.002]. SD detected significantly

more pedunculated or sessile polyps compared to HD [92.8% (142/153) *vs* 79.4% (154/194), p<0.001]. There was no difference in retrieval rate between the two groups. Polyps' endoscopic and histological characteristics are summarized in Table 2.

Table 2. Per polyps analysis of PentaxHiLine vs Olympus-Lucera technologies.

		POLYPS (n=347)				
		HD (n=194)		**SD** (n=153)		**p**
		n	**%**	**n**	**%**	
Polyp Type	*pedunculated*	44	22.7	41	26.8	0.382
	sessile	110	56.7	101	66.0	0.097
	flat	36	18.6	8	5.2	<0.001
	n/a	4	2.0	3	2.0	1.000
Polyp Location	*rectum-sigmoid*	85	43.8	68	44.4	0.914
	left colon	16	8.2	14	9.2	0.848
	transverse colon	42	21.6	37	24.2	0.607
	right colon	48	24.7	33	21.6	0.524
	n/a	3	1.5	1	0.7	0.633
Polyp Size	*≤ 5 mm*	109	56.2	89	58.2	0.744
	6-10 mm	47	24.2	35	22.9	0.800
	>10 mm	30	15.5	26	17.0	0.769
	n/a	8	4.1	3	2.0	0.359
Polyp Histology	*hyperplastic*	33	17.0	27	17.6	0.887
	adenoma	130	67.0	108	70.6	0.487
	cancer	2	1.0	2	1.3	1.000
	n/a	29	14.9	16	10.5	0.261
Polyp Retrieval Rate	*not removed*	9	4.6	3	2.0	0.240
	not retrieved	14	7.2	11	7.2	1.000
	retrieved for histology	166	85.6	137	89.5	0.330
	n/a	5	2.6	2	1.3	0.471

n/a, not applicable

Image or contrast enhancement (i-scan/NBI) were used more frequently in HD patients [23.3% (31/133) versus 12.4% (16/129)] for HD and SD respectively. In order to verify whether magnification add-on might have played play a role in enhancing flat polyps' detection, we compared their use in the flat polyps' population. Forty-four flat polyps were found in 27 patients, 6 using SD and 21 with HD. In the SD flat polyp group, magnification with NBI was used in 3/6 (50%) patients. In the HD group, i-Scan 2 and 3 was used in 13/21 (62%) of the detected flat polyps, showing no statistically significant differences between the two groups (p=0.66). This result suggests that post-processing image or contrast enhancement might not be necessary to identify flat polyps.

Out of 44 flat polyps detected, 26 polyps were adenomas (25 LGD, 1 HGD); among those, 4/26 (15.4%) were identified by SD and 22/26 (84.6%) by HD colonoscopy systems.

Secondary Endpoints

Colonoscopy completion rates were equal in both groups (98.5%). In 4 patients, the caecum was not reached for the following reasons: 1. inflammatory stricture in sigmoid and rectum with SD; 2. obstructive polypoid lesion with SD; 3. test interrupted with HD due to failure of the system; 4. test interrupted at the transverse colon with PHL due to procedural difficulties converted to OL with ScopeGuide and completed.

Total procedure times were comparable: 25.49 ± 12.53 minutes using HD system and 26.65 ± 12.62 minutes using SD. Colonoscopy insertion and normal colonoscopy withdrawal time were similar in the two groups (10.36 ± 5.47 minutes and 16.54±8.12 minutes with HD *vs* 11.04 ± 6.49 minutes and 17.58±8.43 minutes with SD) as well as rectal retroverted view (performed in 57.1% and 53.5% of procedures in HD and SD groups, respectively).

ScopeGuide was used in most patients in the OL group (107/129, 82.9%); nevertheless the endoscopists' perception of procedural difficulties [grade 3: 9.8% (14/133) with PHL *vs* 10.1% (13/129) with OL] and the patients' comfort score were similar using PHL [63.9% (85/133) vs 66.7% (86/129) PHL and OL groups, respectively]. To confirm that the use of the ScopeGuide did not affect endoscopists' difficulty perception and patient comfort, we performed a sub-analysis of these parameters within the OL group comparing the procedures with (107/129) or without (16/129) ScopeGuide. In six patients this was not recorded. Both endoscopists' difficulty perception and patient comfort were comparable [difficulty score 2+3: 65.4% (70/107) *vs* 75% (12/16); comfort score 1 : 66.4% (71/107) *vs* 62.5% (10/16) with or without ScopeGuide respectively].

Comfort score did not appear to be related to sedation since results were comparable between the two optical systems. The average requirements of sedation were as follows: midazolam 1.44±1.05 mg *vs* 1.42±0.83 mg while fentanyl 47.2±31.3 µg *vs* 45.5±27.2 µg in the HD and SD groups, respectively. Buscopan 11.13±9.43 mg (HD group) and 10.74±9.98 mg (SD group) was used at withdrawal in 61% (162/262) colonoscopies with HD or SD. Flumazenil was used in one patient scoped with HD and two patients with SD.

Finally, after pooling the data from the three BCSP centres, the quality assurance indicators for screening colonoscopies were: over 90% bowel preparation described as excellent or adequate (248/262, 94.6%); over 90% unadjusted caecal intubation rate with photographic evidence (258/262, 98.5%); fifteen cancers were detected out of 262 cases (5.7%); ADR ≥ 35% (117/262, 44.6%); mean inspection time over 6 minutes on withdrawal from caecal pole to anus in negative procedures (12.73 ± 7.7 minutes). Retrieval of over 90% polypectomy specimens for histological analysis (303/328, 92.4%); adverse events, such as perforation rate less than 1:1000 colonoscopies (no cases reported) and less than 1:500 colonoscopies where polypectomy is performed (no cases reported), post-polypectomy bleeding less than 1:100 colonoscopies where polypectomy is performed (no cases reported). Only one adverse event was recorded, post procedure hypotension and bradycardia in the HD group which was effectively addressed in the recovery area.

Discussion

Colorectal cancer is the second leading cause of cancer deaths in the UK.[1, 2, 3] Detection of cancer at an early stage, as well as detection and removal of polyps through colonoscopy significantly decreases mortality rate. The principal aim of the BCSP in the UK is to reduce the mortality from colorectal cancer by the early detection of cancerous or pre-cancerous lesions. Screening efficacy requires a high quality examination. The accuracy of colonoscopy in order to identify these lesions is vital to the success of the program. Factors important in the optimization of the test include bowel preparation, operator skill, withdrawal time and image quality.[8, 13, 14, 15, 16, 19]

In the present study, we enrolled patients prospectively at four BCS centres, and colonoscopy data was pooled from six BCSP accredited endoscopists using both systems. Based on our previous data,[26] I-scan 1 was used routinely during withdrawal from the caecum to increase surface enhancement and consequently ADR. In this multi-

site, randomised controlled trial, we aimed to compare directly the performance of SD Olympus Lucera with Scope Guide and the higher resolution Pentax HiLine during colonoscopies performed as part of the BCSP.

The recommended benchmarks for a quality BCSP colonoscopy have been an ADR on screening colonoscopies of at least 15% in women and at least 25% in men.[27] This correlates with other measures of colonoscopic performance such as withdrawal time, caecal intubation rate and longer term outcomes such as interval cancer rate. In this prospective cohort of patients the quality of the programme was demonstrated by a high PDR and ADR, which was similar with both systems. The HD-PHL group resulted in a PDR 55.6% and ADR 43.6%; the SD-OL group outcome was a PDR 56.6% and ADR 45.7%. Most importantly, HD showed an advantage in the detection of flat lesions (18.6% *versus* 5.2%) at the per polyps analysis which seems unrelated to the use of image and contrast tools for enhancement. In particular, NBI was used in 50.0% of the patients with flat polyps scoped by SD-OL and i-Scan 2 and 3 were applied in 62.0% of patients with flat polyps scoped by HD-PHL. However, i-scan-1 was set as a default in all procedures at withdrawal which might provide an explanation for the superior detection in the HD-PHL group.

Polyp morphology and size influence detection rates.[21] Rembacken and colleagues have demonstrated that flat and depressed polyps are less easily identified and therefore are more likely to be missed on colonoscopy.[22, 28] Moreover, it is suggested that the advanced cancers appearing within three years of a negative colonoscopy may have developed from these subtle lesions.[28, 29] Concerning polyp size, a miss rate for advanced adenomas (>1 cm) of up to 6% and as high as 27% in adenomas smaller than 5 mm in size has been recorded.[10, 30, 31] It is plausible that a higher image resolution by improving visibility and polyp detection may also help reduce the rate of missed lesions.

In general, flat and depressed polyps are more likely to contain high-grade dysplasia or invasive cancer than polypoid lesions.[28] This notion has been challenged by recent studies reporting similar or lower frequencies of carcinoma in nonpolypoid lesions than that observed in polypoid lesions.[32, 33, 34] Although the prevalence of advanced histology in flat adenomas is similar to that of polypoid adenomas,[35] flat adenomas are associated with an increased prevalence of synchronous large and advanced adenomas.[36] This could imply the need for shorter surveillance intervals in patients, especially when we consider the unequivocal differences between the epithelia of nonpolypoid and polypoid lesions at the molecular level (i.e., gene expression, genetic and epigenetic alterations).[37]

Several studies have demonstrated the potential advantage of utilising additional optical technology such as virtual chromoendoscopy such as NBI imaging in Olympus scopes to improve polyp detection although results are conflicting.[13, 14, 15, 16] NBI is an image enhancement technology, which improves the visibility of vascular and mucosal structures. The filtered light is absorbed by vessels but reflected by the mucosa and consequently facilitates the detection of tumours, given they are often highly vascularized.[38, 39]

Pentax has developed i-Scan technology to provide digital image modification with enhancement of mucosal and vascular patterns. The HD endoscopes offer the option of using i-scan providing real-time virtual chromoendoscopy. There are three digital algorithms for i-scan: surface enhancement, contrast enhancement, and tone enhancement, designed to enhance surface and vascular patterns to improve optical diagnostic performance. Both surface enhancement and contrast enhancement retain natural colour tones and can be used during the entire procedure.[40, 41]

Preliminary data from a retrospective study at University College Hospital demonstrated that mega pixel (over one million pixels) scopes (PHL) detected more adenomatous polyps than standard definition scopes (OL) in a cohort of 269 patients

within the UK BCSP, without compromising other measures of colonoscopy performance.[26] In this study, we found that a higher proportion of patients had polyps detected when examined with the HD (66%) compared to SD (44%). The median number of polyps detected per procedure was also higher at one (IQR 0-3) for Pentax compared to zero (IQR 0-1) for Olympus (p = 0.01). The median size of polyps was identical at 4 mm in the Olympus group (IQR 2-8) and 3 mm in the Pentax group (IQR 2-8) (p = 0.98). In both groups, approximately one quarter of the polyps were pedunculated and the other three quarters were sessile in nature (p = 0.74). Improved overall polyp detection rate of megapixel high resolution scopes, particularly for small flat adenomas could potentially improve outcomes of the BCSP.[26]

In a previous retrospective study by Chernolesskiy *et al.* in a cohort of 468 patients undergoing colonoscopies within the BCSP, the quality colonoscopy yield indicators were similar with PHL and OL.[42, 43] However, polyp morphology was not analysed and we believe that our data are not discordant with this well-powered study since we also did not find significant performances differences except in detection of flat adenomas.

This advantage of a higher detection rate for flat lesions has the potential to translate a minor rate of missed pathology consequently to improved cancer detection and prevention. Conversely, there were no differences between the two systems in terms of caecal intubation time, caecal intubation rate, total procedure time, withdrawal time, polyp retrieval rate, or immediate/late complications.

Flumazenil was used in one patient scoped with HD and two patients with SD. Our units follow accredited guidelines which suggest recording and investigating any case of oversedation and subsequent treatment with an internal audit of sedation-related complications and the frequency that sedation is used outside of recommended guidelines.[44] Overall, the use of flumazenil to reverse midazolam sedation after endoscopy is generally believed to be safe and efficient by reducing patients' time of stay in the recovery room.[45] However, some studies have shown that the use of flumazenil can increase the risk of adverse effects in patients who are then admitted to the emergency ward with impaired consciousness due to benzodiazepine overdose.[46] Therefore, under closely monitored and regulated environments, the use of flumazenil after endoscopy under conscious sedation can improve the treatment efficiency, but every occasion of its use should be audited.

Finally, our data are similar within the two systems in terms of endoscopist's perception of procedural difficulty, sedation used (type and dose) and patient comfort score despite the use of a Scope guide and variable stiffness in the OL group.. The PHL system does not offer these options, although does have fixed tapered stiffness and was as manoeuvrable and comfortable for both the endoscopists and the patients from our statistical analysis. Nevertheless, one case was switched from PHL to OL with ScopeGuide before completion on the discretion of the endoscopist.

The main limitation of our study is that it is underpowered for the primary outcomes of polyp detection and ADR, because enrolment was suspended before the calculated sample size was reached due to recruitment issues across several sites within the timeframe of the study. Multiple testing could also be a potential limiting factor when interpreting results.[47, 48] A final limitation is the potential inter-operator variability in ADR,[49] not analysed in the present study. Endoscopists with a greater than 20% adenoma detection rate have had a significantly lower rate of interval colorectal cancer,[8] with the operator volume and accreditation as bowel cancer screeners determining adenoma detection rate.[50] Training and quality improvement programs have resulted in an improved adenoma detection rate in those who were randomized to the training program compared to those who were not.[51]

In conclusion, the high definition system improves the flat adenoma detection while offering the same manoeuvrability and patient comfort when compared to standard

definition system. A higher flat polyp detection rate is likely to have a significant impact on the detection of early cancers or high grade lesions, as well as the prevention of colorectal cancer and decreased rate of missed lesions.

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Conflicts of Interest

Pentax Medical have funded other projects at UCLH but no funding was provided directly for this study.

Author Contributions

Simona Di Caro designed the study, analysed the data and contributed to writing the manuscript. Lucia Fini, Roser Vega, and Konstantinos C. Fragkos analysed the data and contributed to writing the manuscript. Sunil Dolwani, John Green, Lesley-Ann Smith, Conrad Beckett, and Ewen Cameron helped design the study, provided data and helped writing the manuscript. Matthew Banks designed and supervised the study, provided data, helped with analysis, and wrote the manuscript.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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