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Clinical utility of capsule endoscopy in gastrointestinal bleeding

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Declaration

I declare that the thesis has been composed by myself and that the work has not been submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Chapter 3 was previously published in Endoscopy as ***Clinical validity of flexible spectral imaging color enhancement (FICE) in small-bowel capsule endoscopy: a systematic review and meta-analysis*** by **Yung DE (student)**, Boal Carvalho P, Giannakou A, Kopylov U, Rosa B, Rondonotti E, Toth E, **Plevris JN (supervisor)**, Koulaouzidis A. This study was conceived by all of the authors. I designed this study, carried out data collection and statistical analysis for this study, as well as preparing it for submission.

The work presented in Chapter 4 was previously published in Expert Review of Gastroenterology and Hepatology as ***The validity of suspected blood indicator software in capsule endoscopy: a systematic review and meta-analysis*** by **Yung DE (student)**, Sykes C, Koulaouzidis A. This study was conceived by all of the authors. I designed this study, carried out data collection and analysis, and prepared the study for submission.

The work presented in Chapter 5 was previously published in Expert Review of Gastroenterology and Hepatology as ***Systematic review and meta-analysis: is bowel preparation still necessary in small bowel capsule endoscopy?*** by **Yung DE (student)**, Rondonotti E, Sykes C, Pennazio M, **Plevris JN (supervisor)**, Koulaouzidis A. This study was conceived by all of the authors. I designed this study, carried out data collection and analysis, and prepared the study for submission.

The work presented in Chapter 6 was previously published in Endoscopy International Open as ***Earlier use of capsule endoscopy in inpatients with melena or severe iron deficiency anemia reduces need for colonoscopy and shortens hospital stay*** by **Yung DE (student)**, Koulaouzidis A, Douglas S, **Plevris JN (supervisor)**. This study was conceived by all of the authors. I designed this study with the assistance of my supervisors, carried out data collection and analysis, and prepared the study for submission.

The work presented in Chapter 7 was previously published in the United European Gastroenterology Journal as ***Capsule endoscopy in young patients with iron deficiency anaemia and negative bidirectional gastrointestinal endoscopy*** by **Yung DE (student)**, Rondonotti E, Giannakou A, Avni T, Rosa B, Toth E, Lucendo AJ, Sidhu R, Beaumont H, Ellul P, Negreanu L, Jiménez-Garcia VA, McNamara D, Kopylov U, Elli L, Triantafyllou K, Shibli F, Riccioni ME, Bruno M, Dray X, **Plevris JN (supervisor)**, Koulaouzidis A, and the Capsule Endoscopy in Young Patients with IDA research group. This study was conceived by all of the authors. I participated in study design, carried out data collection and analysis, and prepared the study for submission.

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Abstract

Introduction

Capsule endoscopy (CE) is a first-line diagnostic tool for known or suspected small bowel bleeding (SBB), and its use has over time been expanded to include panenteric imaging. It offers advantages over conventional endoscopy in minimal invasiveness and ease of use. However several drawbacks remain including the lack of modalities other than imaging, inability to control or propel the capsule, lesser image quality compared to conventional endoscopy and labour-intensiveness of data interpretation.

Aims and objectives

This thesis aims to explore the ways in which use of CE can be optimised in the current clinical or "real world" context, focusing on its use in gastrointestinal bleeding and working within current resource and technological limitations.

Methods

A review and analysis of the existing literature was undertaken, examining the present state of CE technology and identifying current gaps in knowledge. Meta-analyses were undertaken examining the effectiveness of the two main methods of image enhancement in CE: the use of bowel preparation and currently available rudimentary computer-aided diagnosis.

The following studies then looked into how to better select patients who should be prioritised for CE examination – a pertinent issue in today's resource-stretched healthcare systems. A retrospective study was carried out to examine the effects of altering the timing of CE examination in patients referred for likely SBB, using cases carried out at our tertiary care centre over the past decade. Outcomes were compared between patients who had undergone CE following negative bidirectional endoscopies, or negative upper gastrointestinal tract endoscopy only. Furthermore, building on existing work, a second study was undertaken using a prospectively-designed database to collect multicentre data on findings and outcomes in young patients referred for CE with iron deficiency anaemia. This study investigated factors predictive of small bowel neoplasia in this patient group.

Finally, the effect of image visualisation quality on diagnostic certainty was investigated. CE images were processed to alter image parameters, and the resulting images presented to an

international group of expert CE readers in order to determine thresholds for acceptable image quality and the effects of differing image quality in the parameters examined.

Results

Currently-available image enhancement techniques:

(1) Use of bowel preparation: Laxative use did not improve the diagnostic yield of CE with odds ratio (OR) 1.1 for both overall and significant findings when comparing laxative use with pre-procedural fast only. However, subjectively-determined small bowel visualisation quality improved with the use of laxatives (OR 1.60 (95%CI 1.08–2.06)), NNT 14.

(2) Use of suspected blood indicator (SBI): The overall sensitivity of SBI for bleeding or potentially bleeding lesions was 0.553, specificity 0.578, DOR 12.354. The sensitivity of SBI for active bleeding was 0.988, specificity 0.646, DOR 229.89.

(3) Use of FICE digital image enhancement: Overall, the use of the three FICE modes did not significantly improve image delineation or detection rate in CE. For pigmented lesions only, FICE setting 1 performed better in lesion delineation and detection.

Patient selection and CE pathways:

The earlier use of CE in inpatients with melena or IDA, no signs of lower gastrointestinal pathology and negative UGIE resulted in shortened hospital stays, significant diagnostic yield from both small bowel and upper gastrointestinal tract, and two-thirds less unnecessary colon investigations without affecting clinical outcomes.

In young patients (age <50 years) with IDA and negative bidirectional GI endoscopy, the overall diagnostic yield of CE for clinically significant findings was 32.3%. 5% of our cohort was diagnosed with SB neoplasia; lower MCV and weight loss were associated with higher diagnostic yield for significant SB pathology.

Effects of visualisation quality on diagnostic certainty:

Poor visualisation quality in all parameters affected mostly neoplastic lesions. Software to increase contrast and sharpen images can improve visualisation quality; smart frame rate adaptation could improve the number of high-quality frames obtained. Thoroughness in small bowel cleansing was found to be most important when there is suspicion of neoplasia.

Conclusions

The data in this thesis show that CE could be employed earlier in the diagnostic pathway for patients presenting clinically with SBB, as an effective diagnostic and triage tool in the semi-acute setting. Although the overall diagnostic yield of CE is lower in younger patients, young patients with IDA and no significant findings on bidirectional endoscopy are also more likely to have significant small bowel findings, and should perhaps be referred preferentially for CE. This would help increase the efficiency of resource utilisation.

Of the currently available image enhancement techniques in CE, digital image enhancement and diagnostic tools such as SBI and FICE remain of limited validity; however they show the most promise for vascular lesions and active GI bleeding, which supports their use in the acute to semi-acute setting to improve efficiency of CE reading. Image enhancement with both laxatives and digital means is the most crucial when patients are suspected of having more subtle small bowel findings such as small bowel neoplasia.

Lay Summary

Capsule endoscopy (CE) involves a small camera in a pill, which is swallowed by patients and takes several images as it passes through the gut to be excreted naturally. It is used to investigate the small bowel, and is primarily used to look for sources of bleeding and areas of inflammation, but is also now used to image the whole gut. This thesis examines ways of optimising the use of CE in gastrointestinal bleeding.

Ways to enhance CE image quality: Laxatives are commonly used to clear the bowel prior to CE. Analysis of data from several previous studies showed that although laxative use improved visualisation quality in the small bowel by a factor of 1.5x, it did not increase diagnostic yield. Suspected blood indicator (SBI) software automatically selects frames with areas of red pixels to help pick up areas of bleeding. Analysing data from several published studies, SBI was found to have sensitivity of 55% for bleeding or potentially bleeding lesions. However the sensitivity for active gut bleeding was much higher at 98.8%. On the other hand, digital colour alteration with FICE did not significantly improve image visualisation quality or image detection rate.

Patient selection and CE pathways:

Examining data collected at a university teaching hospital showed that the earlier use of CE in inpatients with suspected small bowel bleeding resulted in shortened hospital stays and two-thirds less unnecessary colon investigations, without affecting patient outcomes in our patient group.

Previous research has shown that young patients (age <50 years) with anaemia are more likely to have significant small bowel findings on CE. A larger group of such patients was collected across several teaching hospitals. In young anaemic patients, CE picked up significant findings in was 32.3%. 5% of this group had small bowel tumours. Patients with lower MCV and weight loss were more likely to have significant findings.

Effects of visualisation quality on diagnostic certainty: CE images were modified to reduce visualisation quality in a stepwise manner, focusing on the parameters of image opacity, blurriness and contrast. Expert CE readers were asked determine if they could make a confident diagnosis from these images. Images of small bowel tumours were most affected by poor visualisation quality, compared to images of bleeding vessels or bowel inflammation.

This thesis shows that CE can be an effective diagnostic and triage tool in patients with suspected small bowel bleeding. Although the overall diagnostic yield of CE is lower in younger patients, young patients with anaemia are also more likely to have significant small bowel findings, and should perhaps be referred preferentially for CE. This would help increase the efficiency of resource utilisation. Of the currently available image enhancement techniques in CE, digital image selection and enhancement tools remain of limited usefulness. They are most useful when there is active bleeding in the gut, which supports their use in the acute to semi-acute setting to improve efficiency of CE reading. Image enhancement with both laxatives and digital means is the most crucial when patients are suspected of having more subtle small bowel findings such as small bowel tumours.

Contents

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Abbreviations

ALICE	Augmented Live-body Image Colour-Spectrum Enhancement
ANOVA	analysis of variance
ASGE	American Society of Gastrointestinal Endoscopy
AUC	area under the curve
AVM	arteriovenous malformation
BNF	British National Formulary
CD	Crohn's disease
CE	capsule endoscopy
CI	confidence interval
CR	completion rate (of capsule examination)
CT	computed tomography
DOR	diagnostic odds ratio
DY	diagnostic yield
ESGE	European Society for Gastrointestinal Endoscopy
FICE	flexible spectral imaging colour enhancement
GI	gastrointestinal
Hb	haemoglobin
HDR	high dynamic range
IBD	inflammatory bowel disease
ICV	ileocaecal valve
IDA	iron deficiency anaemia
IQR	inter-quartile range
OGIB	obscure gastrointestinal bleeding
OR	odds ratio
MCV	mean corpuscular volume
MgC	magnesium citrate
MR	magnetic resonance
NaP	sodium phosphate
NBI	narrow band imaging
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
PEG	polyethylene glycol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS	quality assessment of diagnostic accuracy studies (tool)
SB	small bowel
SBB	small bowel bleeding
SBI	suspected blood indicator
SBVQ	small bowel visualisation quality
SROC	summary receiver operating characteristic curve
UGIE	upper GI tract endoscopy
WLE	white light endoscopy

Chapter 1 Introduction

Capsule endoscopy (CE) is a prime imaging modality for the small bowel (SB) introduced to routine clinical practice in the mid-2000s. Images are obtained by a micro-camera as the capsule is propelled through the gastrointestinal (GI) tract by peristalsis; these images are – in most capsule models – transmitted wirelessly to an external receiver, producing a video which is then read and interpreted by clinical staff[1]. Since its introduction, CE has become an invaluable diagnostic tool due to its minimal invasiveness, safety, and ease of use for both clinicians and patients.

1.1 Overview of capsule examination

1.1.1 CE process

A capsule examination involves a pill-sized and shaped camera which is swallowed by the patient in order to image the GI tract. The camera takes multiple sequential images as it passes through the GI tract, usually at a rate of several frames per second. In most models the images are transmitted remotely to an external recorder which the patient must carry on their person for the duration of the examination (see **Table 1.1** for a detailed summary of capsule models). The capsule records for a period of up to 12h, following which the recording device is retrieved and the captured images are downloaded to a capsule reading software platform. The images are strung together to achieve a video of the GI tract, which is then read and reported.

Conventionally, capsule reporting involves identification of key anatomical landmarks allowing the footage to be divided into oesophageal, gastric, small bowel, and colonic segments. The landmarks are: first gastric image, first duodenal image, and first caecal image or ileocaecal valve (ICV). Usually, some comment is made regarding quality of bowel preparation, as this influences diagnostic certainty and overall clinical usefulness of the examination. Reporting of a single CE examination is usually estimated to take 30-90 minutes, depending on complexity of the examination and reader experience[2,3].

At present there remain few guidelines to standardise the capsule reading and reporting process[4], although recent recommendations have been made regarding credentialing for CE

reading and reporting[5–7]. The evidence that these recommendations are based on is moderate at best.

1.1.2 Indications for CE

At present, CE is the main mode of SB investigation, as it is able to access areas beyond the reach of conventional upper GI tract endoscopy (UGIE) and colonoscopy in a minimally-invasive manner – for the oesophagus, stomach and colon, conventional endoscopy remains the gold standard due to the ability to both diagnose and treat, as well as the ability to control the endoscope within the body. Double-balloon enteroscopy, although considered the gold standard for SB visualisation, is a far more invasive and laborious process with proportionally greater risks to the patient and greater demand on resources such as time, medical equipment and manpower.

The strongest clinical indication for CE, which makes up the bulk of CE referrals, is for investigation of suspected small bowel bleeding (SBB), which is currently defined as has previously been referred to as obscure GI bleeding (OGIB) (see **section 1.4**). The next most common indication for CE is for investigation of suspected SB inflammation, usually suspected Crohn's Disease (CD), and similarly for repeat SB visualisation in patients with known CD, to monitor disease progress and response to treatment.

A much less common but nonetheless crucial indication for CE is the investigation of suspected SB malignancy. Although SB tumours are rare and account for only 1-3% of primary GI malignancies[8], their rarity and usually nonspecific presentations mean they tend to be diagnosed late, with approximately 50% having metastasised by the time of diagnosis[9]. Of note, iron deficiency anaemia (IDA) forms a significant proportion of referrals for patients who are eventually diagnosed with SB malignancies. Previous case series and reports have estimated that IDA accounts for 60-100% of indications for SB cancers diagnosed via CE; this is an important indication for which CE may have particular clinical utility[10].

1.2 Imaging capsules currently available

Overall, CE presents certain advantages over more invasive endoscopic techniques, including its safety, ease of use and feasibility[11–13]; therefore, in more recent years the indications for CE have expanded to include upper GI tract imaging with oesophageal and gastric capsules, colon CE and "panenteroscopy" with the Crohn's capsule[14].

For the purposes of this thesis I have included only visual/imaging capsule models. 2 non-imaging capsules are currently commercially available - Motilis®[15] and SmartPill®[16] - which are marketed for investigation of gut motility and physiology, but these are not discussed here due to their vastly different nature. **Table 1.1** provides a summary of the currently available capsule models on the market.

Table 1.1: Current commercially available capsule models and their specifications

Model	Pillcam® SB3	Pillcam® ESO3	Pillcam® Colon2	Pillcam® Crohn's Capsule	MiroCam® MC1000 series	MiroCam® MC2000	Endocapsule® 10	OMOM®	CapsoCam® SV1	NaviCam
Manufacturer	Medtronic (Given Imaging Ltd)				Intromedic		Olympus	JinShan Science and Technology Co, Ltd	Capso Vision Inc.	Ankon Technologies Co, Ltd
Clinical (marketed) use of capsule	SB imaging	Oesophageal imaging	Colon imaging	Panenteric imaging in Crohn's disease	SB imaging Apart from MiroCam® Navi (part of MC1000 series) for stomach imaging		SB imaging	SB imaging	SB imaging	Magnetically-controlled stomach imaging
Mass(g)	3.0	2.9	2.9	2.9	3.25	Ns	3.3	<6	ns	<5
Dimension(mm)	11x26	11x26	11x31	11.6x32.3	10.8x24.5	10.8x30.1	11x26	13x27.9	11x31	28x12
Battery(h)	≥8	0.5	10	10	12		12	8±11	15	≥8
Illumination	4 LED	2x4 LED	2x4 LED	2x4 LED	6 LED		6 LED	6 LED	16 LED	Ns
Field of view(°)	156	172	172	168	170		160	140±10	360	140
Depth of field(mm)	0-30	0-30	0-30	0-30	7-20		0-20	0-35	0-30	0-30
Number and type of cameras	1xCMOS	2xCMOS			1xCMOS	2xCMOS	1xCCD	1xCMOS	4xCMOS	1xCMOS
Image Resolution	320x320	256x256	ns	Na	320x320		1920x 1080	QVGA VGA	N/A	480x480
Image Sampling rate (fps)	2-6	35	4 -35	4-35	3-6	3	2	2 QVGA 0.5 VGA	3-5 per camera	Ns
Image enhancements available	Blue mode, FICE, SBI	-	-	-	ALICE, HDR	HDR	-	SBI	-	-
Image/frame selection technology available (to reduce reading times)	Yes (Quickview)	No	No	Yes	No	Yes (Express view)	No	Automatic removal of similar consecutive frames	No	No

Adaptive frame rate	Yes	No	Yes	Yes	No	No	No	Yes	No
Need for external receiver	Yes				Yes	Yes	Yes	No	Yes
Data transmission	RF				Electric field propagation	RF	RF	On-board EPROM flash	RF

Abbreviations : CMOS complementary metal-oxide-semiconductor, LED light emitting diode, ns not specified, RF radiofrequency, SBI suspected blood indicator

1.3 Use of CE in small bowel bleeding (SBB)

1.3.1 Definition of SBB

SBB, defined as recurrent and/or persistent GI bleeding from a source which remains unidentified following negative bidirectional GI endoscopy, is currently the strongest and most common clinical indication for performing CE[17]. It presents as iron deficiency anaemia (IDA) and/or melaena[18,19], and has previously been referred to as OGIB, a term recommended now only for patients in whom the source of bleeding remains unclear following GI investigation[20].

1.3.2 Current guidelines

Current guidelines recommend the use of CE following negative bidirectional GI endoscopy in patients with SBB[20–22]. However, the available evidence underlying these guidelines is classed as "moderate" at best by the European Society for Gastrointestinal Endoscopy (ESGE), and few existing studies have evaluated the accuracy parameters (e.g. sensitivity, specificity, positive predictive value and negative predictive value) of CE[21]. This may be due to the lack of a suitable and accessible "gold standard" for comparison – although the ESGE suggests that intraoperative endoscopy is the ideal standard for evaluation of CE, such a study is relatively un-feasible to carry out.

Overall, the diagnostic yield of CE in OGIB/SBB is estimated to be 60-70%[20,21], implying that a significant proportion of 30-40% patients remain undiagnosed following CE. Previous work carried out prior to initiation of this thesis has however shown that CE has clinical value if even for prognostication – patients with negative CE are half as likely to re-bleed compared to those with positive findings on CE[19].

1.4 Use of CE in iron deficiency anaemia (IDA)

1.4.1 Definition of IDA

Anaemia is defined by the World Health Organisation as haemoglobin concentrations (Hb) below 130mg/L in men and 120mg/L in non-pregnant women over 15 years old; however the definition of iron deficiency varies in the literature and is generally based on markers including mean corpuscular volume (MCV), serum iron and transferrin levels, transferring

saturations and ferritin. Current guidelines recommend that barring the presence of significant overt non-GI blood loss, GI investigation is warranted in all male and postmenopausal female patients[23].

Patients who present with isolated IDA and no obvious or overt signs of GI bleeding are a particular subset of patients with SBB who often present diagnostic and management difficulties. In the developed world, IDA in general is estimated to affect about 5-10% of premenopausal women and 2-5% of men and postmenopausal women[24,25]. Therefore, it accounts for up to 13% of GI referrals, representing a significant burden of GI disease and gastroenterologists' workload[23,26]. Despite the increased uptake of bidirectional GI endoscopy in the diagnostic evaluation of IDA, a significant 30-50% of patients remain undiagnosed[26].

In these patients, guidelines based on moderate to weak evidence[23] suggest an initial trial of treatment with iron supplementation. Further direct SB visualisation is not recommended unless there are symptoms suggestive of SB disease or in refractory IDA; however anecdotally it is now routine to perform CE in patients following negative bidirectional endoscopy, where SBB is suspected.

1.4.2 IDA and patient demographics

Previous CE studies have shown that the aetiology of GI blood loss differs with patient demographics. Although younger patients (conventionally defined as age 50 years and below) form a smaller proportion of patients referred for CE with suspected SBB, the small amount of available evidence suggests that they are more likely to have significant findings. Young patients are more likely to bleed from SB malignancies, Dieulafoy lesions, Meckel's diverticula, polyps or Crohn's Disease (CD). Conversely, those older than 40 are more likely to have angioectasias or non-steroidal anti-inflammatory drug (NSAID)-induced ulceration[27–29]. SB tumours (or malignancies) have a prevalence of 3-9% in patients undergoing SB evaluation[30,31] and although uncommon, they are of particular importance due to their poor prognosis. Furthermore, an increasing incidence of SB malignancy has been documented over the past few decades[32,33].

Therefore, under the current guidelines, younger patients may be at risk of delayed diagnosis,

which could adversely impact outcomes[34]. Moreover, to the best of our knowledge, only a few studies focusing on young IDA patients undergoing SB evaluation are available to date[28,29,35]. Therefore questions raised include whether younger patients presenting with SBB should be fast tracked for CE, as well as how to assess bleeding potential and/or clinical significance of small bowel findings in order to guide further management.

1.5 Use of CE in GI bleeding outside of the SB

CE is usually performed non-acutely for the aforementioned indications as an outpatient procedure. Commonly, such patients tend to be admitted and stabilised (if necessary), investigated with an urgent upper GI endoscopy, and discharged to await further investigation. However, there is emerging evidence that performing CE closer to the index bleeding episode increases its diagnostic yield, within the suggested time frame of 14 days. More recent work suggests that in SBB the maximum diagnostic yield for CE is achieved within the first 72h of presentation[36]. This is corroborated by studies showing that for the same indications, inpatient CE has a higher diagnostic yield compared to outpatient procedures [37–39]. Unfortunately there is overall scarce data on the inpatient use of CE (**Table 1.2**).

Although current practice varies, guidelines generally suggest performing CE in patients presenting acutely with suspected SBB only following both negative upper and lower GI endoscopy (i.e. negative bidirectional endoscopy). Performing colonoscopy in the acute setting is a demanding task both for the patient and clinician, and is often limited by the quality of bowel preparation and patient fitness or tolerance. At our large tertiary care hospital, there has recently been a trend for performing CE following a negative index upper GI endoscopy (UGIE) alone, with anecdotal evidence that by doing so unnecessary colonoscopies have been avoided in a proportion of patients. This is an area which perhaps merits further investigation, which this thesis therefore aims to explore.

Table 1.2: Summary of previous studies on inpatient use of CE

Authors, Year[ref]	Type of study	CE procedure	Patients	Findings
Dunnigan *et al*, 2007[40] (abstract)	Retrospective, single centre	NS	Inpatients: 22 Outpatients: 133	CE incomplete in 50% of inpatients and 23.5% outpatients; inpatient status significantly associated with incomplete CE
Robinson *et al*, 2011[37]	Retrospective, multicentre	PillCam®SB2, PEG, no simethicone, prokinetics as indicated	Inpatients: 167 Outpatients: 540	Significant findings, endoscopic placement, nongastric passage and incomplete CE more likely in inpatients. Inpatients had longer GTT, were more likely to be male and have overt bleeding.
Lepileur *et al*, 2012[38]	Retrospective, multicentre	PillCam®M2A, PEG	Inpatients: 137 Outpatients: 774	Predictive factors for positive CE: males, >60 years old, overt bleeding, inpatients
Yazici *et al*, 2012[39]	Retrospective, single centre	PillCam®SB, no laxative preparation	Inpatients: 70 Outpatients: 264	Inpatients were older, more likely to have overt bleeding, and active bleeding was more commonly found in inpatients. CE completion rate significantly lower in inpatients and patients with GI bleeding; prolonged GTT and SBTT in inpatients. Results amplified when looking only at ICU inpatients vs general ward patients.
Singh *et al*, 2013[36]	Retrospective, single centre	PillCam®SB/SB2, no laxative preparation	Inpatients: 144 Outpatients: 116 (all patients having CE for overt OGIB)	Early use of CE within 3 days of admission associated with higher diagnostic yield, therapeutic intervention rate and reduced length of stay.

Abbreviations: CE capsule endoscopy; GTT gastric transit time; ICU intensive care unit; OGIB obscure gastrointestinal bleeding; SBTT small bowel transit time; NS not specified

1.6 Limitations of CE

1.6.1 Limited scope for enhancement of visualisation quality

Many limitations remain which curtail the wider adoption and use of CE. A significant limitation is that CE remains an entirely visual mode of investigation in the context of GI bleeding – any type of multimodal capsule has yet to progress far beyond the developmental or experimental stage into mainstream usage.

The overall positive diagnostic yield for SB disease using CE is approximately 60%[41]. The largest concern, as in most modes of investigation, is that the capsule may miss crucial lesions such as ulcers and submucosal tumours and/or other SB malignancies[42–45]. Bar the Ankon gastric capsule, the vast majority of commercial CE devices – and all SB capsules – are passively propelled by gut peristalsis. Visualisation of the entire length of SB is achieved in 80–90% of patients[21,46], while the lack of control over capsule propulsion leads to an estimated 30% of discrete lesions being missed, especially when there is increased gut motility or if an image of a lesion is captured in only one brief frame[47,48].

Most developments and variations in CE have focused on changing the configuration of cameras, for example putting cameras around the body of the capsule rather than on the end, as in Capsocam, or putting two heads on a capsule as in the Pillcam® Colon and Crohn's capsules. Although proprietary capsule reading software includes various methods of post-capture image enhancements such as the ability to increase contrast (common to almost all capsule reading platforms), to enhance certain wavelengths of light (as in FICE imaging), or to make shades of red stand out more (as in the OMOM software), all these methods depend heavily on the quality of the original image captured by the cameras.

Therefore, the utility of CE is also limited by capsule size, which affects the amount of battery and processing power which can be included. At present, CE imaging quality has yet to meet the standards of conventional endoscopy, let alone enhanced imaging, even though battery life, resolution and field of vision have improved over time. Despite substantial improvement in image quality in recent years, particularly in image resolution, the image pixelation of capsule models remains disappointingly low[49,50], especially when compared with that of conventional high definition flexible endoscopes.

1.6.2 Capsule reading and reporting

Capsule reading and reporting is a time- and labour-intensive process. A single CE examination generates lengthy video footage which makes it time and labour-intensive to interpret; this affects the utility of an examination, especially when considering its use in the acute to semi-acute setting.

Computer-assisted diagnosis remains elusive. Although software has been developed to help with identification of pathology, these methods remain mostly unvalidated and unproven by larger, robust studies. There are two main types of software available to aid CE reading: (1) image/video enhancing software to improve the visualisation and pickup of pathology[51], and (2) image selection software which selects frames from a CE video for further review, thus reducing the number of frames or segments the human CE reporter has to view.

(1) Image enhancing software

Examples of image enhancing software include basic image adjustments common to all capsule reading and reporting software– mainly brightness and contrast. Proprietary software includes FICE and blue mode for PillCam® and ALICE for Mirocam® (which also offers high dynamic range (HDR) capability).

Blue mode has previously been discussed[52–55] whilst there is scant data available on ALICE[56] and QuickView[57–60]; therefore in this thesis, I have focused on FICE and SBI, which have the largest body of data and represent examples of the two main groups or types of software.

(2) Image selection software

Examples of image selection software include the SBI, PillCam®'s QuickView and Mirocam®'s Express View option. Also in their early stages are novel machine learning algorithms for the automated detection of pathology in endoscopic images[61,62]; again, such technology has yet to become fully developed, well-validated and readily available.

Because CE is at present an entirely visual mode of investigation, current developments to improve its utility have focused on not only improving image quality but also increasing the amount of data generated from a single investigation (for example with increased and adaptive frame rate, longer battery life and larger data storage), with the belief that increasing the amount of information obtained will improve its diagnostic abilities. Conversely, this potentially creates a form of information overload and reader fatigue,

therefore making it all the more important that computer-aided diagnosis becomes available and reliable. Developmental computer-aided diagnostic software has already proven useful in other modes of endoscopy, including the use of deep learning and convolutional neural networks for polyp detection in colonoscopy, and also for optical biopsy to aid identification of higher risk polyps and early gastric cancer[63]. Indeed, CE may prove ideal for the development of such software precisely because of the vast amounts of often quite-repetitive data generated in a single capsule examination.

Overall, however, until more efficient ways of CE reading and reporting can be developed and made mainstream, the more judicious selection of patients undergoing CE may improve the efficiency of this mode of investigation, although unanswered questions about when and how to best employ CE remain[21,64].

1.6.3 Need for bowel preparation

Finally, bowel preparation prior to CE examination is still required, to reduce the amount of luminal content and ensure clear mucosal views. However, the optimal pre-CE bowel preparation remains a much-debated topic amongst users worldwide. Several regimes have been proposed using different laxatives, dosages and administration timings; conversely, other clinicians prescribe a clear liquid diet for 24-48h prior to CE with a pre-CE overnight fast, without the use of laxatives.

Those in favor of laxative preparation argue that laxatives improve image quality and SB mucosal visualisation, therefore potentially increasing diagnostic yield[65,66]. Furthermore this appears to offer the clinician better control over bowel emptying. Conversely, those advocating the use of only a clear liquid diet and pre-procedural overnight fast believe that this achieves adequate visualization with superior patient acceptability[67]. Laxative bowel preparation is often the most unpleasant part of endoscopic investigations for patients, and is also particularly difficult for frailer patients who may struggle to cope with the diarrhoea, consequent dehydration and potential electrolyte imbalances. However, frail patients may also more often be considered for CE as opposed to conventional endoscopy due to its minimally-invasive nature, lack of requirement for sedation and east of use.

Perhaps due to the controversial nature of this topic and wide range of clinical opinions, a good number of meta-analyses have been carried out[68–71]. However, several more articles with contradictory conclusions have since been published and a re-examination of the data may be of use.

Chapter 2 Aims and Objectives

This thesis aims to explore the current limits of CE in the clinical or "real world" context, examining ways in which its use can be optimised in conventional clinical settings. This is perhaps especially pertinent in the context of increasingly stretched healthcare systems with limitations on both monetary resources and manpower.

For the purposes of this thesis, I have elected to focus on the indication of GI bleeding as it forms the largest group of patients referred for CE.

The following areas were identified for further investigation:

2.1 Current image enhancement technologies in CE

The currently-available methods for image enhancement in CE – both clinical, using bowel preparation, and digital – will be explored to determine their effectiveness and identify specific areas for future development.

For digital image enhancement methods, I have chosen to focus on FICE as the currently most widely-studied example of image enhancement software and SBI as an example of frame/image selection software.

The use of bowel preparation is also investigated as this is the main way in which image quality can be clinically influenced and is also a topic currently under some debate amongst CE users.

2.2 Use of CE in the acute/semi-acute setting for GI bleeding

This thesis will then examine the role of CE in the diagnostic pathway for patients presenting acutely with potential SBB. This chapter focuses on patients with signs of upper- to mid-GI tract bleeding (melaena and/or IDA), following negative UGIE.

This is based on the clinical experience at our tertiary care centre, where an early CE examination has sometimes been used as both a diagnostic and triage tool in patients who present with signs of more proximal GI bleeding but no significant findings on upper GI endoscopy. Therefore, I have aimed to gather objective data to support or refute this practice.

2.3 Patient selection and prioritisation for CE examination

As previously discussed, in elderly patients with signs of SBB the most likely diagnosis is that of vascular lesions in the SB, and therefore a conservative approach is sometimes more appropriate in these patients. Conversely, younger patients presenting with isolated IDA are a relatively small but significant group of patients who present diagnostic difficulties.

Also building on previous work carried out at our centre which suggested that younger patients with IDA were more likely to have significant SB pathology, this next section aimed to investigate CE findings and outcomes in a larger, multicentre group of young patients referred for CE with iron deficiency anaemia, and especially to identify factors predictive of significant small bowel findings in this patient group.

2.4 Effect of image and visualisation quality of CE images

Much has been said about how CE is limited as it is a solely visual mode of investigation, and there is much discussion about methods to improve the quality of images obtained. However, there is at present little standardisation in how to quantify image quality in CE reporting; this presents certain barriers to transmission of information for both clinical and research purposes. I therefore aimed to examine the contribution of various image parameters to the perception of visualisation quality in CE images.

Chapter 3 Systematic review and meta-analysis: FICE image enhancement in CE

Chapters 3 to 5 detail meta-analyses carried out to investigate the currently available methods for image enhancement in CE. In this chapter, I aim to establish the clinical effectiveness of FICE, which is perhaps the most widely-available and -used digital image enhancement software in CE reading and reporting, and therefore a good representation of this class or type of image enhancement techniques.

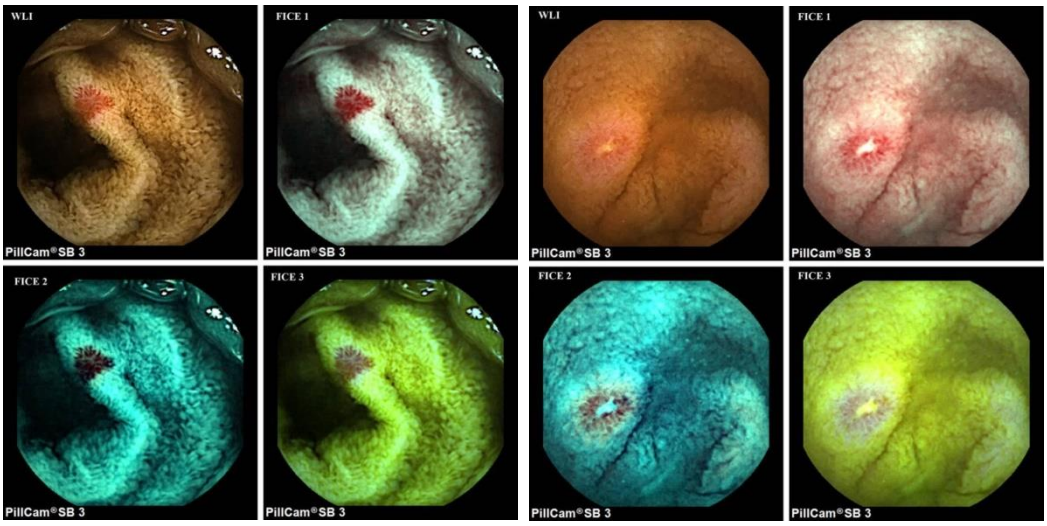
3.1 Introduction: FICE

Flexible spectral imaging color enhancement (FICE; also Fujinon Intelligent Chromo Endoscopy; Fujinon, Saitama, Japan) is a digital processing algorithm which takes white-light endoscopy (WLE) images and mathematically processes the image by emphasizing certain ranges of wavelengths. Three single-wavelength images can be selected and assigned to red, green, and blue (RGB) monitor inputs to display a composite color-enhanced image (**Table 4.1**, **Figure 4.1**)[51]. FICE virtual chromoendoscopy is hypothesized to enhance surface patterns, improving visualization and detection of mucosal lesions[72]. FICE has been applied to endoscopy of the upper and lower GI tract, as well as in double-balloon enteroscopy[73,74], with the aim of increasing detection of neoplastic lesions. However, there remains a lack of conclusive evidence for its clinical effectiveness in enhancing lesion visualization and detection in CE[75].

Table 3.1: Wavelengths (in nm) for each of the FICE modes used in RAPID® capsule reading software

Mode	Red	Green	Blue
FICE 1	595	540	535
FICE 2	420	520	530
FICE 3	595	570	415

Figure 3.1: (a) Angioectasia and (b) SB ulcer, as visualised with white-light imaging and FICE settings 1-3 (left to right, top to bottom)



(a) Angioectasia images
Top L: Original image
Top R: FICE setting 1
Bottom L: FICE setting 2
Bottom R: FICE setting 3

(b) SB ulcer images
Top L: Original image
Top R: FICE setting 1
Bottom L: FICE setting 2
Bottom R: FICE setting 3

3.2 Methods

3.2.1 Search strategy

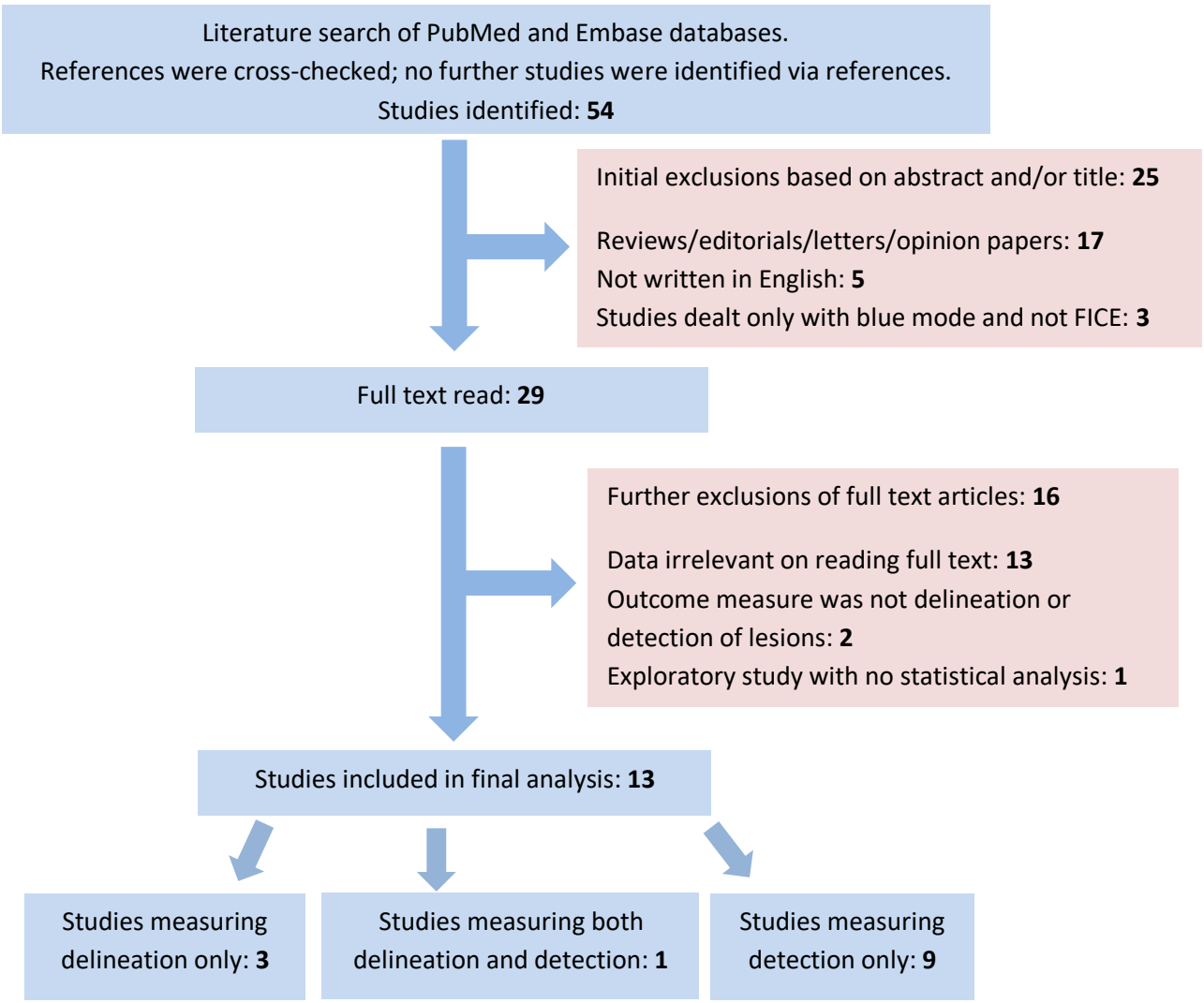
A comprehensive literature search was conducted using the PubMed and Embase databases (January 2000 to November 2015). The search was performed on December 12 2015. In order to capture as many full-text articles and abstracts as possible, a broad search strategy was employed, using the terms “capsule endoscopy,” “small-bowel,” “FICE,” and “chromoendoscopy” in various combinations. The initial search was performed with no limitations. Primary selection was based on titles and abstracts; further selection involved reading the full texts of any relevant publications (**Figure 3.2**).

For a study to be included for meta-analysis, the following inclusion criteria were defined: (a) complete articles published in English; (b) articles where CE was used to investigate small-bowel pathology only; and (c) articles where one or more of the three FICE modes was used on CE images and/or videos. Studies had to have investigated: (i) changes in image delineation or (ii) changes in lesion detection, using FICE.

Data extraction and quality control were performed independently by myself and a second reviewer, so that cross-checking could be carried out. Data from included articles were extracted into a predefined data collection sheet for collation and comparison. A third reviewer, expert in capsule endoscopy and the content material, was involved if there was any uncertainty about the data or discrepancies. When additional data were required, primary (first and/or senior) authors of the specific manuscript(s) were contacted by email with relevant questions.

This study adhered to the PRISMA checklist (http://www.prisma-statement.org) as a standard.

Figure 3.2: Study selection for studies examining use of FICE in CE



3.2.2 Outcome measures

Lesion delineation

This was defined as the pooled rate of improvement in lesion visualization based on reader rating (individual or average), as measured against the original WLE image for: (a) each of the FICE modes, and (b) the two main pathological findings consistently presented across all studies: angioectasias and small-bowel mucosal ulcers/erosions.

Images where visualization was deemed similar to or worse than with WLE were grouped together as "lack of improvement."

Lesion detection

This outcome measure examined whether there was any significant difference between the average number of lesions detected across the three FICE modes and the white-light mode, for angioectasias and mucosal ulcers/erosions. This technique was used in studies where each CE video was viewed only once by one reader.

3.2.3 Statistical analysis

Data on the DY of CE were extracted, pooled, and analysed. Where sufficient data were available for analysis (i.e. 3 or more studies available with relevant data), pooled results with corresponding 95% CIs were derived using the fixed effects model (Mantel–Haenszel method) unless significant heterogeneity was detected, in which case, a random effects model (DerSimonian–Laird) was used. The Q statistic of χ^2 test and I^2 were used to estimate the heterogeneity of individual studies contributing to the pooled estimate. I^2 values were used to evaluate whether the differences across the studies were greater than could be expected by chance alone. A P value <0.05 suggests the presence of heterogeneity beyond what could be expected by chance alone. I^2 values of 20%–50% or of >50% suggest moderate and high heterogeneity, respectively. Forest plots were constructed for visual display of individual study and pooled results[76].

Sensitivity analyses were generally conducted firstly by examining forest plots to identify significant outliers, and by systematic exclusion of studies to assess whether this caused significant shifts in results. Further analyses of relevant subgroups were also attempted if adequate data were available.

Repeated-measures analysis of variance (ANOVA) was used to measure the difference in lesion detection between WLE and the three FICE modes based on the findings from the videos in WLE mode and using FICE settings 1–3. The F statistic was used to determine significance in repeated-measures ANOVA. $P < 0.05$ for the F-statistic was considered statistically significant[77]. Statistical analysis was performed by using the Metan package of STATA version 12.1 (StataCorp, College Station, Texas, US).

3.2.4 Assessment of study bias

Methodological quality and potential bias of the included studies was evaluated by using the QUADAS-2 scale[78]. The use of FICE was the "index test" and CE imaging or video review under WLE was taken to be the "reference standard."

3.3 Results and meta-analysis

3.3.1 Search results and included study characteristics

The initial search yielded 54 publications (**Figure 3.2**) of which 39 were excluded for the following reasons: articles were reviews/editorials/letters/opinion papers (n = 17); data found to be irrelevant on reading of full text (n = 13); not in English language (n = 5); studies which dealt exclusively with other chromoendoscopy techniques (e.g. Blue mode) and not FICE (n = 3); outcome measure not delineation or detection of lesions (n = 2)[79,80]; study was exploratory with no statistical analysis (n = 1)[81].

Eventually, 13 studies were included (**Table 3.2**)[54,73,90–92,82–89]. The countries of origin for the studies were: Japan (n = 7)[73,82,83,86–89], Portugal (n = 4)[84,85,90,92], Belgium (n = 1)[91], and the United Kingdom (n = 1)[54]. All studies were conducted using PillCam®SB 1 and/or 2 (Medtronic, Minnesota, USA) and most used experienced readers, usually defined as having read >100 capsule endoscopies.

Two sets of studies were identified as coming from the same hospitals. Two studies from the Imagawa et al. group were used for two separate analyses, one for delineation[82] and one for detection[73]. Therefore there was no overlap in the data used in these two studies. Another three studies[84,90,92] were carried out by the same group of researchers at the same center; these were confirmed by direct contact with one of the study authors to have used completely separate patient groups with no overlap.

Table 3.2 (a): Summary of studies measuring lesion delineation as an outcome

Authors, Year[ref]	Country	Type of CE	No. of readers	Experience of readers	No. of images	FICE 1			FICE 2			FICE 3		
Angioectasias						**Improved**	**Similar**	**Worse**	**Improved**	**Similar**	**Worse**	**Improved**	**Similar**	**Worse**
Krystallis, 2011[54]	UK	PillCam® SB1/2	2	1 moderate (>50 CEs), 1 experienced (>500 CEs)	18	14	2	2	5	3	9	1	7	10
Imagawa, 2011 (GIE)[82]	Japan	PillCam® SB1	5	NS	23	20	3	0	20	2	1	1	22	0
Sato, 2014[83]	Japan	PillCam® SB1/2	5	Experienced (>100 CEs)	152	Outcome measured by average of VAS from readers with positive scoring for "improved" and negative scoring for "worse"; breakdown not specified. Average VAS for FICE 1: 72.7±5.2			Average VAS for FICE 2: 74.0±14.9			Average VAS for FICE 3: 58.7±14.9		
Cotter, 2014[84]	Portugal	PillCam® SB2	2	Experienced (>200 CEs)	39	38	1	0	38	1	0	18	18	3
Ulcers/Erosions														
Krystallis, 2011[54]	*As above*				60	22	6	32	2	8	50	2	4	54
Imagawa, 2011 (GIE)[82]					47	26	19	2	12	32	3	0	34	13
Sato, 2014[83]					88	Average VAS for FICE 1: 72.9±5.4			Average VAS for FICE 2: 67.9±5.7			Average VAS for FICE 3: 53.5±6.5		
Cotter, 2014[84]					49	31	12	6	28	10	11	12	18	19

Abbreviations: CE capsule endoscopy; FICE Fuji Intelligent Colour Enhancement; GIE Gastrointestinal Endoscopy (journal); NS not specified; VAS visual analogue score

Table 3.2 (b): Summary of studies measuring lesion detection as an outcome

Authors, Year[ref]	Country	Type of CE	No. of readers	Experience of readers	No. of videos	Study design	No. of lesions determined by reference	No. of lesions under WL	No. of lesions under FICE 1	No. of lesions under FICE 2	No. of lesions under FICE 3
Angioectasias											
Imagawa, 2011 (SJG)[73]	Japan	PillCam® SB2	2	Experienced (>50 CEs)	50	1 reader for WL, 1 for FICE	NA	17	48	45	24
Duque, 2012[85]	Portugal	PillCam® SB2	4	Experienced	20	1 reader for WL, 1 for FICE	NA	32	NA	35	NA
Kobayashi, 2012[86]	Japan	PillCam® (NS)	3	NS	24	All videos and modes seen by all readers	NA	Average lesions per video ± SD: 21±2.6	25.7±3.2	22.0±3.0	22.7±2.1
Matsumura, 2012[87]	Japan	PillCam® SB1/2	2	Experienced	81	All videos and modes seen by all readers	14	Average lesions per video ± SD: 2±1.5	2±1.4	1.3±0.5	4±1.2
Sakai, 2012[88]	Japan	PillCam® SB2	4	No previous CE experience	12	Crossover*; each video in each mode read once only	60	26	40	38	31
Konishi, 2014[89]	Japan	PillCam® SB2	5	Experienced	10	All videos and modes seen by all readers	NA	Average lesions per video ± SD: 0.58±0.15	0.92±0.2	0.72±0.18	0.74±0.2

Sato, 2014[83]	Japan	PillCam® SB1/2	3	Experienced (>100 CEs)	50	Crossover	NA	17	24	33	18
Boal Carvalho, 2016[90]	Portugal	NS	4	Experienced (>100 CEs)	60	Crossover	54	26	54	NA	NA
Ulcers/Erosions											
Imagawa, 2011 (SJG)[73]	*As above*						NA	32	40	54	51
Duque, 2012[85]							NA	24	NA	41	NA
Kobayashi, 2012[86]							NA	Average lesions per video ± SD: 14±0.0	19.3±2.3	15.3±1.2	11.3±4
Matsumura, 2012[87]							24	Average lesions per video ± SD: 1.9±1.9	3.3±2.3	3.6±3.4	1.9±1.2
Sakai, 2012[88]							82	38	62	60	20
Konishi, 2014[89]							NA	Average lesions per video ± SD: Erosions 3.3±4.29; Ulcers 1.66±4.00	Erosions 8.65±8.55; Ulcers 4.86±12.9	Erosions 11.94±15.12; Ulcers 5.6±14.51	Erosions 3.54±4.03; Ulcers 2.9±8.50
Sato, 2014[83]							NA	28	22	41	24
Boal Carvalho, 2016[90]							17	15	17	NA	NA

Studies where Saurin Score used (types of lesions not specified)											
Gupta, 2011[91]	Belgium	PillCam® SB2	2	Moderate experience (about 70 CEs)	60	Crossover	131 P0: 15 P1: 41 P2: 75	NA	All 3 FICE modes used together. P0: 20 (reader 1), 27 (reader 2) P1: 37, 55 P2: 60, 72		
Dias de Castro, 2015[92]	Portugal	PillCam® SB1/2	1	Experienced (>200 CEs)	42	1 reader for all videos	All videos initially "negative" for cause of GI bleeding	NA	14 remained negative, 19 P1 lesions, 2 P2 lesions, 7 with both P1&2	NA	NA

*Example of "*crossover*" study: Reader 1 viewed group A of videos under WL only, then group B under FICE 1. Reader 2 viewed group A under FICE 1 only and group B under WL only. Therefore each video is seen by only 1 reader for each mode.

Abbreviations: CE capsule endoscopy; FICE Fuji Intelligent Colour Enhancement; SD standard deviation; SJG Scand J Gastroenterol (journal); WL white light

3.3.2 Lesion delineation

Improvement in delineation of capsule endoscopy images of lesions was investigated in 4 studies[54,82–84]. Of these, 1 study[83] was excluded from further analysis; the use of a visual analogue scoring system meant that the results could not be entered into the meta-analysis.

Only the use of FICE setting 1 on images of angioectasias appeared to produce a higher rate of improved delineation, with 89% of images considered improved, whereas 45% of images of ulcers/erosions were considered improved using FICE 1. FICE 2 improved delineation in 43% of images of angioectasias. For images of angioectasias in FICE 3 and images of ulcers/erosions in FICE 2 and 3, negligible proportions of images were considered to show improved delineation (**Table 3.3**, **Figures 3.3 and 3.4**).

Heterogeneity of studies was high with I^2 >90% in 4/6 analyses carried out.

Table 3.3: Pooled proportions of "improved" images for each FICE mode (95% CI)

FICE mode	FICE 1	FICE 2	FICE 3
Angioectasias (N=80)	0.89 (0.69-1.08)	0.43 (0.32-0.54)*	0.05 (0.04-0.07)*
Ulcers/erosions (N=156)	0.45 (0.38-0.52)*	0.04 (0.03-0.05)*	0.04 (0.03-0.04)*

* denotes statistical significance

Figure 3.3: Pooled proportions of images of ***angioectasias*** considered to show "improved" visualization under FICE: (a) FICE 1; (b) FICE 2; (c) FICE 3.

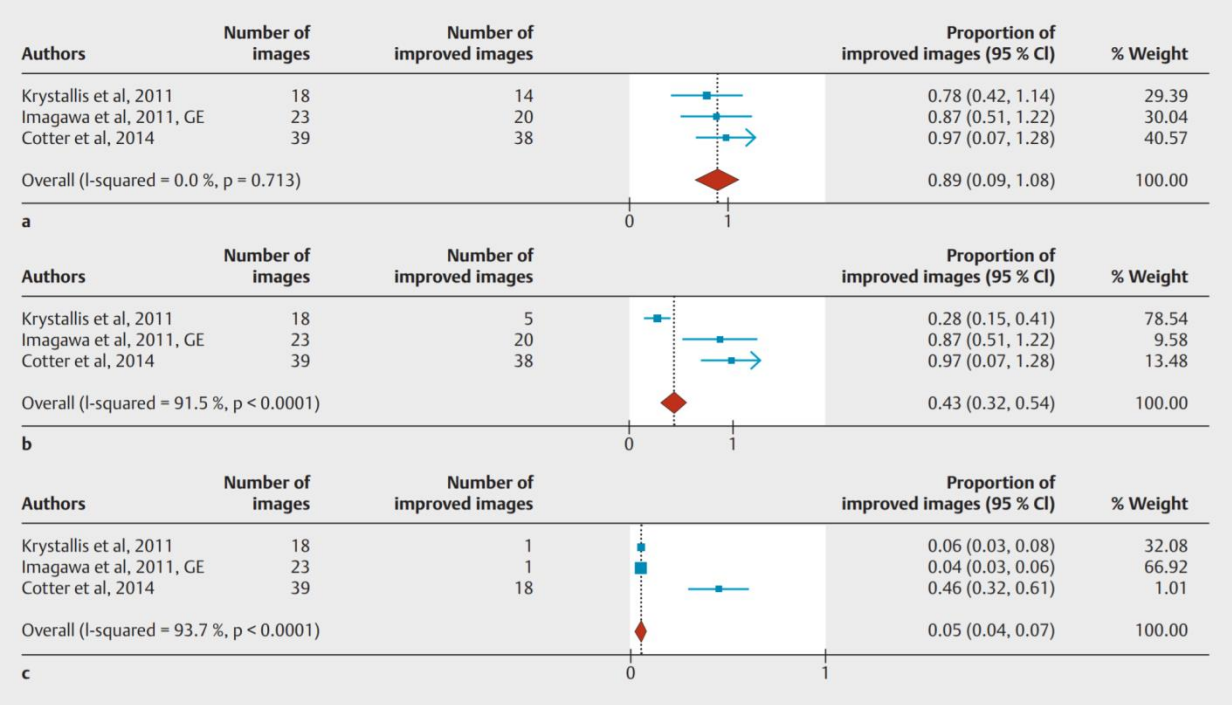
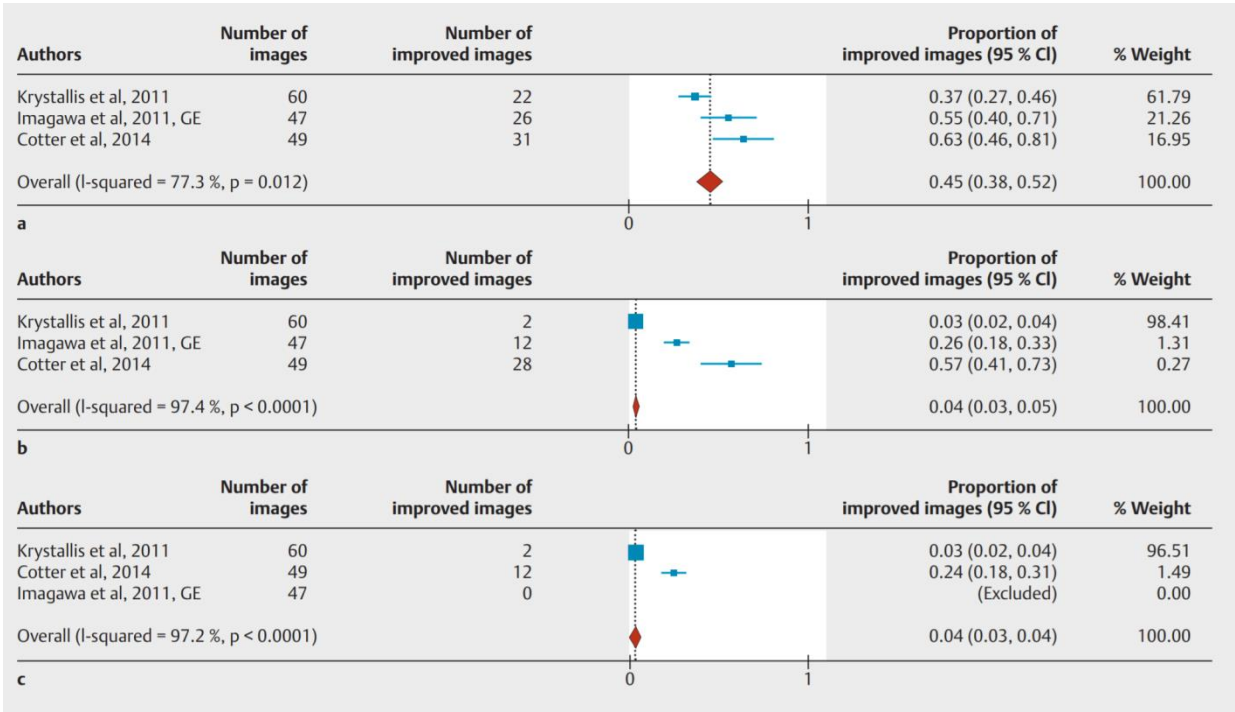


Figure 3.4: Pooled proportions of images of ***ulcers/erosions*** considered to show "improved" visualization under FICE: (a) FICE 1; (b) FICE 2; (c) FICE 3.



3.3.3 Lesion detection

A total of 10 studies[73,83,85–92] measured improvement in detection of lesions. Of these, 3 studies[86,87,89] reported results as average numbers of lesions identified by multiple readers and could therefore not be included in analysis. Another 2 studies[91,92] did not give results by types of lesions, instead using the Saurin score[93]; these could not be included for statistical analysis as the numbers of angioectasias and ulcers/erosions remained unknown.

The remaining 5 studies were designed such that each video in each mode was viewed only once by one reader over the course of the study[73,83,85,88,90]. Therefore these were entered into the analysis, and ANOVA was carried out using the average number of lesions detected per video (**Table 3.4**). The F statistic for the difference in detection of angioectasias and ulcers/erosions in the three FICE modes compared to WLE had a P value >0.05 for both types of lesions, showing that the detection of these lesions did not differ significantly between any of the FICE modes and WLE.

Table 3.4 (a): Repeated measures ANOVA for detection of ***angioectasias***

	SS	Df	MS	F
Between	1.02	3	0.34	1.146
Within	20.179	16	1.261	
-Error	3.559	12	0.297	
-Subjects	16.62	4	4.155	
Total	21.199	19		

F-Statistic	Critical Value	Result	Conclusion
1.146	3.4903	Do not reject the null hypothesis.	The compared groups do not differ significantly, F(3,12) = 1.146, *P* > 0.05.

Table 3.4 (b): Repeated measures ANOVA for detection of ***ulcers/erosions***

	SS	df	MS	F
Between	3.467	3	1.156	1.723
Within	41.093	16	2.568	
-Error	8.052	12	0.671	
-Subjects	33.041	4	8.26	
Total	44.56	19		

F-Statistic	Critical Value	Result	Conclusion
1.723	3.4903	Do not reject the null hypothesis.	The compared groups do not differ significantly, F(3,12) = 1.723, *P* > 0.05.

Abbreviations: SS sum of squares (variability); Df degrees of freedom; MS mean sum of squares

3.3.4 Quality analysis of included studies

The majority of the included studies were of high quality (**Table 3.5**). The main risk of bias identified was recall bias in studies where videos were viewed in more than one mode by the same reviewer.

Table 3.5: Quality of studies and risk of bias as determined by QUADAS-2 assessment.

Author, year [ref]	**Item 1: Risk of bias in pt selection?**	**Item 2: Representative pt spectrum?**	**Item 3: Risk of bias in conduct or interpretation of index test (use of FICE)?**	**Item 4: Applicability of index test to review question?**	**Item 5: Risk of bias from conduct or interpretation of reference standard (WL and/or expert review)?**	**Item 6: Is the use of the reference standard appropriate?**	**Item 7: Risk of bias from flow/timing of study?**
Gupta, 2011[91]	+	+	+	?	+	+	+
Imagawa, 2011 (GIE)[82]	?	+	+	+	+	+	+
Imagawa, 2011 (SJG)[73]	?	+	?	+	+	+	?
Krystallis, 2011[54]	+	+	?	+	+	+	+
Duque, 2012[85]	+	+	+	?	+	+	+
Kobayashi, 2012[86]	?	+	?	+	+	+	+
Matsumura, 2012[87]	?	+	?	+	+	+	+
Sakai, 2012[88]	?	+	+	?	+	+	+
Cotter, 2014[84]	+	+	?	+	+	+	?
Konishi, 2014[89]	+	+	+	+	+	+	+
Sato, 2014[83]	?	+	+	+	+	+	+
Boal Carvalho, 2015[90]	+	+	+	+	?	+	+
Dias de Castro, 2015[92]	?	+	+	?	+	+	+

3.4 Discussion

3.4.1 Limitations of existing CE technology

The technological limitations of CE mean that targeted focus on small-bowel lesions or areas of interest is not possible; any focus occurs only for the amount of time allowed by bowel movement and propulsion[94]. Furthermore, despite recent substantial improvements in image quality, particularly image resolution, the image pixellation of SBCE remains disappointingly low[50,95], especially when compared with that of conventional high definition flexible endoscopes. This often leads to suboptimal lesion imaging and therefore potentially reduces the diagnostic yield of capsule endoscopy[14,96]. Software such as FICE, already established in conventional GI endoscopy, has been integrated into commercially available capsule endoscopy reviewing software (RAPID; Medtronic) in order to increase visualization and detection rate for small-bowel findings. However, clinical opinion and anecdotal evidence remain divided as to the usefulness of FICE and other chromoendoscopy software for capsule endoscopy review[97].

3.4.2 Usefulness of FICE modes

In this meta-analysis, all three FICE modes failed to show any statistically significant improvement in visualization of small-bowel pathology. Although with FICE setting 1 a pooled proportion of 89% of angioectasia images were considered “improved” (defined as improved visualization aiding lesion characterization and enhanced delineation of lesion surface and/or borders), compared with the WLE images, this was not statistically significant. For small-bowel angioectasias viewed under FICE 2 and 3, and for mucosal ulcers/erosions viewed under all three FICE modes, less than 50% of the images were considered to be improved. In fact, for FICE modes 2 and 3, there was close to no improvement in ulcer/erosion visualization compared with WLE imaging.

Therefore, FICE appears to perform well when there is significant color alteration of the lesion, as in angioectasias. This could be partially explained by the fact that pigmented fluids, such as blood and bile, allow the greatest contrast with small-bowel mucosa even under WLE. FICE further enhances this contrast, leading to subjective improvement in visualization, whereas it may not perform as well with nonpigmented lesions[73,97]. The most recent technical report from the American Society for Gastrointestinal Endoscopy (ASGE) states that

there is no evidence for an optimal FICE mode for tissue diagnosis and differentiation in conventional GI endoscopy[51].

Spada et al. defined the clinical usefulness of chromoendoscopy in terms of the following criteria: (i) improvement in lesion detection rate; (ii) improvement in lesion delineation; and (iii) ability to identify lesions which require treatment[97]. In fact, the number of lesions detected on full video reading may be a more accurate index of the clinical performance of FICE against WLE because of the unambiguous binary response of pathological finding detected or not. This approach is likely to be less subjective than assessment of delineation improvement as determined by human readers. The majority of pathological findings at capsule endoscopy consist of vascular lesions and mucosal defects. Polypoid or submucosal lesions, where software tools can enhance diagnostic accuracy[62,98], are found less frequently.

Therefore, in the video studies examining detection rate for small-bowel pathological findings, FICE did not produce any significant improvement in the detection of angioectasias or mucosal ulcers/erosions, compared to WLE video reading. Furthermore, all these studies relied on human vision and perception for detection of lesions. Psychological studies have shown that the colour red produces a stronger reaction in humans, therefore human readers may be more likely to pick up on red-coloured lesions (i.e., blood or vascular lesions) compared to the more muted green and brown tones in FICE modes 2 and 3[99–101]. By extension, narrow band imaging (NBI) is based on the penetration properties of different wavelengths of light corresponding to the two light absorption peaks of haemoglobin, so as to increase the contrast and therefore visibility of vasculature[51]. The results of this meta-analysis are similar overall to those achieved in studies on the use of virtual chromoendoscopy in conventional GI endoscopy: the value of virtual chromoendoscopy lies in aiding lesion visualization and therefore characterization, rather than in increasing detection[51]. Although all but one of the studies included in this meta-analysis involved experienced capsule endoscopy readers, a recent study found that using FICE and Blue mode also helped beginner capsule endoscopy readers to better characterize lesions[53], suggesting that this may be an area warranting further investigation.

3.4.3 Comparison with other digital image enhancement techniques

This review and meta-analysis has focused on FICE alone, although other virtual chromoendoscopy software is currently available such as Blue mode[51] and Augmented Live-body Image Color-Spectrum Enhancement (ALICE) (Intromedic, Seoul, South Korea)[56]. However, the existing body of data is small and too heterogeneous for more systematic analysis. Although in this meta-analysis FICE has not performed as well, there is some evidence for the usefulness of other forms of virtual chromoendoscopy, mainly Blue mode[52,54,55,59]. Current evidence suggests that Blue mode remains a more user-friendly form of virtual chromoendoscopy which can be applied with ease to full video readings. However, none of the existing studies have shown a meaningful increase in diagnostic yield with Blue mode. Interestingly, Aihara et al. presented a study using image-enhanced capsule endoscopy which increased the contrast between the surrounding mucosa and lesions such as vascular or inflammatory lesions or polyps. They reported that the effects of this contrast capsule are similar to those of NBI in conventional GI endoscopy[102]. The only study using ALICE, presented as an abstract, reported improved visibility of flat and depressed small-bowel lesions[56].

3.4.4 Limitations

Limitations of this meta-analysis include, firstly, the heterogeneity of current published studies investigating the usefulness of FICE, as shown by the high I^2 values. These studies varied considerably in terms of study design, selected population, images and videos for analysis, and models of capsule endoscope used with their subsequent effect on technical performance. For instance, differences in the LED specifications between the PillCam® versions could vary the image quality and interpretation between studies. The heterogeneity of study design meant that several could not be included in the meta-analysis, thus greatly limiting the sample size. None of the included studies reported whether the readers had been tested for color blindness; it is unclear whether this could influence intraobserver agreement. The majority of the studies included in this meta-analysis also did not specify the size or clinical significance of the lesions, another factor which could influence detection rate.

3.5 Conclusions

FICE 1 seems to perform better for pigmented lesions such as angioectasias, both in lesion delineation and detection. However, the evidence is equivocal as to whether FICE 2 and 3 aid CE reading. Overall, the use of the three FICE modes did not significantly improve detection rate or the quality of visualisation of the most common pathological findings seen on CE.

Chapter 4 Systematic Review and meta-analysis: Suspected Blood Indicator

The previous chapter examined the data for FICE as a method of digital image enhancement in order to improve image quality and diagnostic ability. As previously discussed, the other major type of software available to aid capsule reading is that of image or frame selection software. This chapter aims to investigate the clinical effectiveness of suspected blood indicator (SBI) software in selecting video frames which could potentially represent GI bleeding and flagging these frames or video segments up for review, as it represents the main type of image selection software in CE reading.

4.1 Introduction: SBI

The SBI is an image selection feature developed by Medtronic® as part of its RAPID® CE reading software. It tags video frames with red pixels which could represent possible areas of haemorrhage in the GI tract. Similar software is available using the OMOM VUE platform and also for the Olympus Endocapsule®. However, the clinical usefulness of SBI is debatable; although the few published studies suggest it has a sensitivity of up to 80% in active GI bleeding, it appears to have a much lower sensitivity (around 25%) for lesions with bleeding potential but not bleeding at time of imaging. Therefore, the overall sensitivity and specificity is estimated at 40-60%[103,104]. Furthermore, there is very limited data on the use of SBI in CE reading and no conclusive analysis of its accuracy parameters.

4.2 Methods

4.2.1 Search strategy

A comprehensive literature search was conducted using the databases PubMed and Embase on the 20th of August 2016, capturing articles from January 2000 until the search date. The search terms used were “capsule endoscopy” (both as keyword and MeSH term) AND “suspected blood indicator” (as keyword as no MeSH term was available). The search was performed with no limitations.

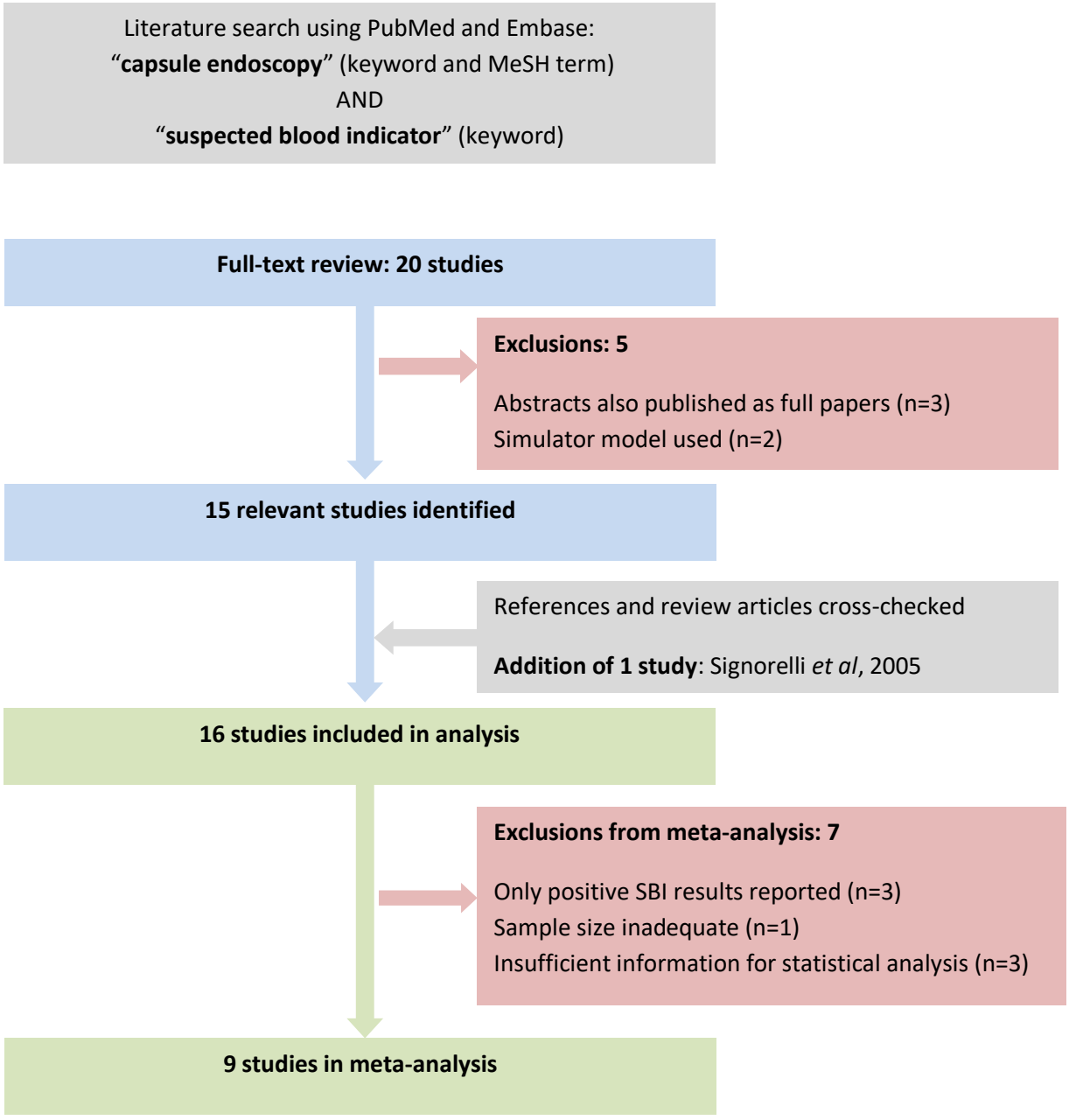
Initial screening of publications was carried out via title and keywords. Following identification of potentially relevant articles, full text selection was carried out according to the inclusion and exclusion criteria detailed below. References were manually cross-checked to ensure no publications had been missed. A flowchart detailing study selection is shown in **Figure 5.1**.

The inclusion criteria were: observational and case-control studies of the use of SBI in CE cases, encompassing all areas of the GI tract, both prospective and retrospective, articles published in English. Exclusion criteria were: systematic reviews and/or meta-analyses, editorials, opinion papers, reviews, studies where SBI was not used in actual patients.

Data extraction and quality control were performed independently by myself and a second author. A third reviewer, expert in the content material, was involved if any conflict occurred. Where additional data were required, attempts were made to contact the primary (first and/or senior) or corresponding authors of the relevant manuscript(s) via electronic mail.

This study adhered to the PRISMA checklist (http://www.prisma-statement.org) as a standard.

Figure 4.1: Study selection for studies examining use of SBI in CE



4.2.2 Outcome measures

The diagnostic accuracy (sensitivity, specificity, diagnostic odds ratio (DOR)) of SBI software for the diagnosis of GI bleeding was evaluated. For each study, the numbers of true positive, true negative, false positive and false negative results were listed. CE findings reported by human reviewers were considered the reference standard.

4.2.3 Statistical analysis

The bivariate model was used for data summary, following which parameter estimates from the model were used to obtain summary receiver operating characteristic curves (SROC) depicting test accuracy via the relationship between sensitivity and specificity[105]. The closer the curve approaches the 45-degree diagonal of the SROC space, the less accurate the test. The area under the curve (AUC) represents test accuracy, ranging from 0.5 (poor accuracy) to 1.0 (excellent accuracy). Similarly, index Q* corresponds to the uppermost point on the SROC where sensitivity equals specificity; the range of values is the same as that of the AUC. Only direct test comparisons were performed.

I^2 was used to estimate the heterogeneity of individual studies contributing to the pooled estimate[76]. Due to high statistical heterogeneity overall, the DerSimonian-Laird random effects model was applied. The effects of heterogeneity between studies were assessed using sensitivity analyses of the following subgroups: studies investigating small bowel bleeding only, studies investigating active bleeding only, studies where results were reported using full CE examinations rather than individual lesions and the exclusion of studies at high risk of bias as defined by QUADAS-2.

The QUADAS-2 scale was used to evaluate quality of the included studies[78]. The “index test” was SBI and human CE readers taken to be the “reference standard”. Item 7 was considered “not applicable” as any time difference between analysis by readers and with SBI would not affect results. Analyses were conducted using Meta-DiSc 1.4 software[106] (Ramon y Cajal Hospital, Madrid, Spain).

4.3 Results and meta-analysis

4.3.1 Search results and included study characteristics

The PubMed search yielded 10 results with 6 relevant articles identified. Embase search yielded 31 results, included all 6 articles identified from PubMed search. In total 20 articles were tagged as relevant.

Three abstracts[60,107,108] were excluded as they were later published as full papers[58,109,110] which were included in this analysis. Another 2 articles[111,112] were excluded as they used a simulator model and not actual patients.

One more study was identified through manual reference review[104]; this was likely to have been missed in the initial search due to title wording. Therefore, 16 studies were eventually identified as relevant for further review.

The included studies are summarised in **Table 4.1**. The 16 studies included[58,103,118–123,104,109,110,113–117] had been published between 2003 and 2016. Countries of origin were: USA (n=6)[58,103,110,113,120,121], and 1 each from Australia[123], Canada[114], France[122], Germany[109], India[118], Italy[104], South Korea[116], Portugal[119], Spain[115], UK[117]. Nine were abstracts[113–121] and 7 had been published as full papers[58,103,104,109,110,122,123]. Only one study was multicentre[122]. Seven were prospective[113,115,117,118,121–123] while 9 were retrospective[58,103,104,109,110,114,116,119,120].

Table 4.1: Summary of studies examining SBI in CE

Authors, Year[ref]	Country	Single/ Multi-centre	Retro/Pro-spective	No. of pts	No. of CEs	CE model	SBI software versions	Indications for CE	No. of readers	Experience of readers	Active bleeding only or potentially bleeding lesions considered	Location of lesions	Agreement between full CE video and SBI or agreement per lesion	TP (positive SBI and bleeding/ lesion seen by reader)	FP (positive SBI but no bleeding/ lesion seen by reader)	TN (negative SBI and no lesion/ bleeding seen by reader)	FN (negative SBI but bleeding/ lesion seen by reader)
Gross, 2003[113] (Abstract)	USA	Single	Prosp	72	72	NS	Given, NS	Post-transfusion pts only	NS	NS	Active bleeding	Small bowel	Full video	16	1	55	0
Liangpunsakul, 2003[103]	USA	Single	Retro	24	24	M2A®	NS	NS	5 initial; findings confirmed by another 2	Experienced	Both	Small bowel & stomach	Per lesion	28	3	17	81
Zanati, 2004[114] (Abstract)	Canada	Single	Retro	42	42	M2A®	NS	NS	NS	NS	Both	Small bowel	Per lesion	18	41	NS	NS
D'Halluin, 2005[122]	France	Multi	Prosp	156	156	M2A®	RAPID, NS	OGIB	NS	>50 CEs	Both	Small bowel	Full video	28	26	68	34
Kitiyakara, 2005[123]	Australia	Single	Prosp	9	9	M2A®	NS	OGIB	NS	NS	Both	Non-small bowel	Full video	6	0	0	1
Signorelli, 2005[104]	Italy	Single	Retro	100	95	M2A®	RAPID, NS	All*	4	All >100 CEs	Both	Small bowel	Full video	27	12	29	39
Ponferrada Diaz, 2006[115] (Abstract)	Spain	Single	Prosp	57	57	M2A®	NS + QV	All	2	Experienced	NS	Small bowel	Full video	These values were not given; 40 CE videos had findings by readers and 17 CE videos were positive on SBI.			
Jeen, 2007[116] (Abstract)	South Korea	Single	Retro	96	96	NS	RAPID, NS	Overt OGIB	2	Expert	Both	NS	NS which was used for calculation of accuracy parameters	31 (lesions)	40 (lesions)	NS	128 (lesions)

Buscaglia, 2008[108]	USA	Single	Retro	287	287	M2A®	RAPID, NS	All	5 initial; findings confirmed by 1 more reader	>50 CEs	Both	Small bowel	Full video	44	139	70	34
Beejay, 2009[117] (Abstract)	UK	Single	Prosp	347	347	NS	NS	All	NS	NS	Both	Small bowel	Per lesion	10613	7076	NS	NS
Reddy, 2010[118] (Abstract)	India	Single	Prosp	38	34	PillCam® SB	RAPID Reader 4	OGIB	1	NS	Both	NS	NS	These values were not calculable given information in abstract; accuracy parameters were only reported as percentages.			
Stein, 2014[58]	USA	Single	Retro	98	116	NS	RAPID Reader 6.0 + QV	OGIB	2 as reference, then SBI compared to 2 other readers	Reference readers experienced, 2 readers using SBI were novices (25 CEs)	Active bleeding	Small bowel	Full video	28	63 (reader 1); 61 (reader 2)	25 (reader 1); 27 (reader 2)	0
Tal, 2014[109]	Germany	Single	Retro	199	199	PillCam® SB2	RAPID Access 6	All	3 + 1 reading with SBI	>100 CEs each	Active bleeding	Small bowel	Full video	42	137	20	0
Barbosa, 2015[119] (Abstract)	Portugal	Single	Retro	300	300	NS	NS + QV	OGIB	2	NS	Both	Small bowel	Full video	37	0	212	51
Han, 2015[120] (Abstract)	USA	Single	Retro	115	115	NS	RAPID Reader 6.0	Overt OGIB	NS	NS	Active bleeding	Whole gut	Full video	115	0	NS	NS
Han, 2016[121] (Abstract)	USA	Single	Prosp	100	100	NS	RAPID Reader 6.0	OGIB	NS	NS	Active bleeding	NS	Full video	18	0	82	0

Abbreviations: CE capsule endoscopy; FN false negative; FP false positive; pts patients; NS not specified; OGIB obscure gastrointestinal bleeding; prosp prospective; QV QuickView®; retro retrospective; SBI suspected blood indicator; TN true negative; TP true positive; UK United Kingdom; USA United States of America

* "All" indications for CE refers to the inclusion of all conventional indications including OGIB, suspected inflammatory bowel disease, suspected neoplasia, coeliac disease, polyposis syndromes etc.

In total, this analysis comprised 2040 patients who underwent 2049 CE examinations. The most frequently used capsule model was M2A® (Medtronic, USA) (7 studies, 670 examinations)[103,104,110,114,115,122,123]; 2 studies used PillCam®SB/SB2 (233 CE examinations)[109,118]. In 7 studies[58,113,116,117,119–121] the model of capsule was not specified. The SBI software used was RAPID® version 6 (4 studies, 530 CE examinations)[58,109,120,121] and RAPID® version 4 (1 study, 34 CE examinations)[118]. Eleven studies did not specify the software used[103,104,123,110,113–117,119,122].

In 5 studies with 985 CE examinations[104,109,110,115,117], the indications for CE were mixed. They included all CE cases done at the various centres e.g. referrals for OGIB, suspected inflammatory bowel disease, and suspected small bowel neoplasia. Nine studies (998 examinations)[58,113,116,118–123] included only CE examinations done for OGIB. Out of these, 2/9 studies (211 examinations)[116,120] included only patients with overt OGIB. One of these nine studies (72 examinations)[113] examined only post-transfusion patients. Two studies did not specify the indications for CE[103,114].

The number of CE readers ranged from 1-6 (not specified in 7 studies). In 8/9 studies, the readers were "experienced" to "expert"[58,103,104,109,110,115,116,122] although the level of CE reading experience was quantified in numbers in only 4 studies[104,109,110,122]. In one study[58], the performance of SBI was compared to novice CE readers with only 25 CEs' experience. Interobserver agreement was reported in only 3 studies[58,104,110]; all 3 reported excellent agreement.

In 11 studies[58,104,123,109,110,113,115,119–122], results were considered true positives if there was at least one lesion in each video flagged by both the SBI and the readers. Therefore not all lesions in each CE examination needed to be picked up by the SBI in order for the examination to be considered true positive. Conversely, 3 studies[103,114,117] reported results as the agreement between SBI and readers for each individual lesion. The method of determining SBI accuracy was unclear in 2 studies[116,118].

Three studies used both SBI and QuickView®[58,115,119]. Another 3 studies reported only positive SBI results[114,117,120].

In 5 studies (602 examinations)[58,109,113,120,121], only active bleeding was considered a positive finding. Ten studies (1390 examinations)[103,104,110,114,116–119,122,123] included both active bleeding

and potentially bleeding lesions. One study[115] did not specify what was counted as a positive finding.

Ten studies (1671 examinations)[58,104,109,110,113–115,117,119,122] reported small bowel findings only. Two studies reported any findings in the entire gastrointestinal tract[103,120]. One study[123] reported only non-small bowel findings. In 3 studies, this information was not specified[116,118,121].

4.3.2 Quality analysis of included studies

Overall, 4 studies[103,104,109,110] were considered good quality (i.e. at low risk of bias, based on QUADAS-2 analysis), 7 were moderate in quality[58,114,115,117–119,122] and 5 were at high risk of bias[113,116,120,121,123]. There were many significant sources of bias identified. The largest potential source of bias was in patient selection, due to those studies which included only patients with OGIB and specifically overt OGIB; this could falsely increase diagnostic yield. Many studies were also unclear about whether the readers were aware of SBI results when reading CEs. QUADAS-2 analysis is summarised in **Table 4.2**.

Table 4.2: QUADAS-2 results for the included studies. Item 7 of QUADAS-2 is not applicable in this meta-analysis.

Author, year[ref]	**Item 1: Risk of bias in pt selection?**	**Item 2: Representative pt spectrum?**	**Item 3: Risk of bias in conduct or interpretation of index test (SBI)?**	**Item 4: Applicability of index test (SBI) to review question?**	**Item 5: Risk of bias from conduct or interpretation of reference standard (CE)?**	**Item 6: Does the target condition match the review question?**	**Overall risk of bias**
Gross, 2003[113]	⊖	?	+	+	?	?	⊖
Liangpunsakul, 2003[103]	+	+	+	+	?	+	+
Zanati, 2004[114]	?	+	+	+	⊖	?	?
D'Halluin, 2005[122]	?	+	?	+	+	+	?
Kitiyakara, 2005[123]	?	+	+	+	⊖	?	⊖
Signorelli, 2005[104]	+	+	+	+	+	+	+
Ponferrada Diaz, 2006[115]	+	+	+	+	⊖	+	?
Jeen, 2007[116]	⊖	?	+	+	?	+	⊖
Buscaglia, 2008[108]	+	+	+	+	?	+	+
Beejay, 2009[117]	⊖	+	+	+	?	?	?
Reddy, 2010[118]	?	+	+	+	?	?	?
Stein, 2014[58]	⊖	+	+	+	+	?	?
Tal, 2014[109]	+	+	+	+	+	+	+
Barbosa, 2015[119]	⊖	+	+	+	?	?	⊖
Han, 2015[120]	?	+	+	+	?	?	?
Han, 2016[121]	⊖	+	+	+	?	?	⊖

4.3.3 Meta-analysis

Seven of the 16 studies could not be meta-analysed. The reasons are as follows: Three studies (504 CE examinations)[114,117,120] reported positive SBI results only with no corresponding group of negative SBI cases, one study had only 7 patients[123] and another three studies (with 187 CE examinations)[115,116,118] did not provide a sufficient breakdown of results and no contact information was available.

The CE examinations in Stein et al[58] were counted twice as the performance of SBI was compared to two separate readers. This was in contrast to all other studies where SBI was compared to a single reference standard, i.e. the consensus of readers, or this information was not specified.

A summary of meta-analysis results is detailed in **Table 4.3**.

Table 4.3: Summary of meta-analysis results

Subgroup	No. of studies	No. of CE examinations*	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
OVERALL	9	1582	0.553 (0.510-0.596)	0.578 (0.547-0.608)	12.354 (3.297-46.297)
Active bleeding only	5	903	0.988 (0.956-0.999)	0.646 (0.610-0.680)	229.89 (20.748-2547.3)
Only moderate to good quality studies	7	1410	0.523 (0.478-0.567)	0.515 (0.482-0.548)	4.327 (1.442-12.989)
Small bowel findings only	7	1353	0.613 (0.564-0.660)	0.535 (0.503-0.568)	9.650 (2.404-38.738)
Studies where any match between SBI and reader per examination/video was considered true positive	8	1453	0.629 (0.581-0.675)	0.573 (0.542-0.603)	17.139 (3.855-76.193)
M2A® only	4	679	0.403 (0.349-0.460)	0.505 (0.453-0.558)	1.370 (0.697-2.691)

Abbreviations: CE capsule endoscopy, CI confidence interval, DOR diagnostic odds ratio

*Note that the CE examinations from Stein *et al* are counted twice as the performance of SBI was compared to 2 separate CE readers.

The overall sensitivity of SBI for any bleeding or potentially bleeding lesions was 0.553 (95%CI 0.510-0.596), **Figure 4.2(a)**. The specificity was 0.578 (95%CI 0.547-0.608), **Figure 4.2(b)**, and DOR 12.354 (95%CI 3.297-46.297). The studies displayed high heterogeneity with I^2 values above 80%. The SROC for the overall sensitivity and specificity of SBI is shown in **Figure 4.2(c)**; the AUC (0.878) and Q* (0.809) both show good accuracy.

However, the sensitivity of SBI for active bleeding only was 0.988 (95%CI 0.956-0.999), **Figure 4.3(a)**. The specificity of SBI for active bleeding was 0.646 (95% 0.610-0.680), **Figure 4.3(b)**, DOR 229.89 (95%CI 20.748-2547.3). The SROC for SBI in active bleeding shows excellent accuracy in this scenario with AUC 0.993 and Q* 0.966, **Figure 4.3(c)**.

When only moderate to good quality studies (based on QUADAS-2 analysis) were included, the sensitivity of SBI was 0.523 (95%CI 0.478-0.567), **Figure 4.4(a)**, specificity 0.515 (95%CI 0.482-0.548), **Figure 4.4(b)**, and DOR 4.327 (95%CI 1.442-12.989). The SROC for SBI in the moderate to good quality studies, **Figure 4.4(c)**, shows a relatively poor performance of SBI with low AUC (0.755) and Q* (0.697).

4.3.4 Sensitivity analyses

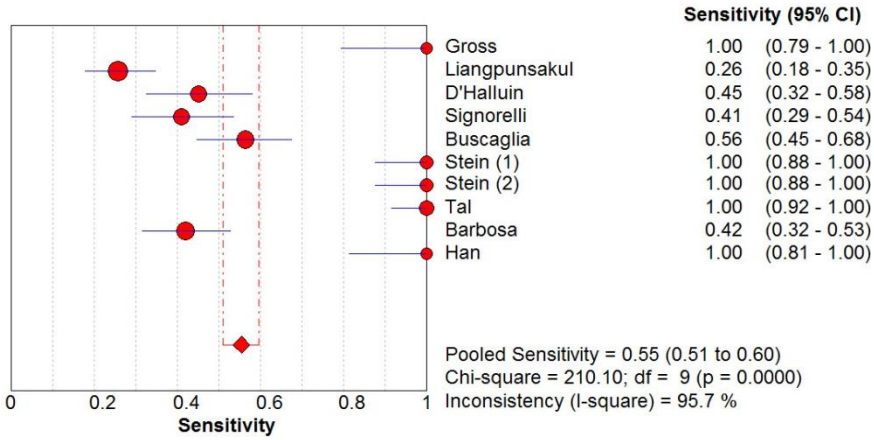
The sensitivity of SBI for small bowel findings was similar at 0.613 (95%CI 0.564-0.660), specificity 0.535 (95%CI 0.503-0.568) and DOR 9.650 (95%CI 2.404-38.738).

In the studies where a single match between SBI and reader per examination/video was considered a true positive, results remained similar with sensitivity 0.629 (95%CI 0.581-0.675) and specificity 0.573 (95%CI 0.542-0.603). The DOR for this group was 17.139 (95%CI 3.855-76.193).

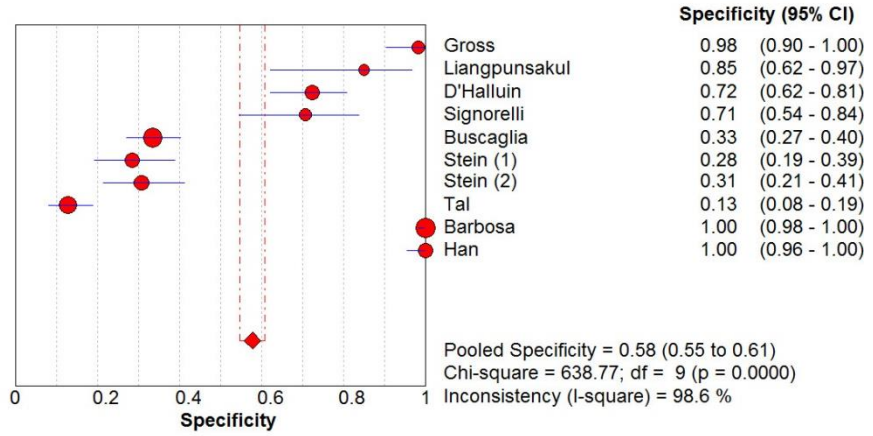
In the studies using the first version of PillCam® (M2A®), the sensitivity was poorer at 0.403 (95%CI 0.349-0.460), specificity 0.505 (95%CI 0.453-0.558) and DOR 1.370 (95%CI 0.697-2.691).

Figure 4.2: Pooled measures of diagnostic accuracy of SBI for ***all lesions with bleeding potential and active bleeding***. (a) sensitivity; (b) specificity; (c) SROC curve

(a)



(b)



(c)

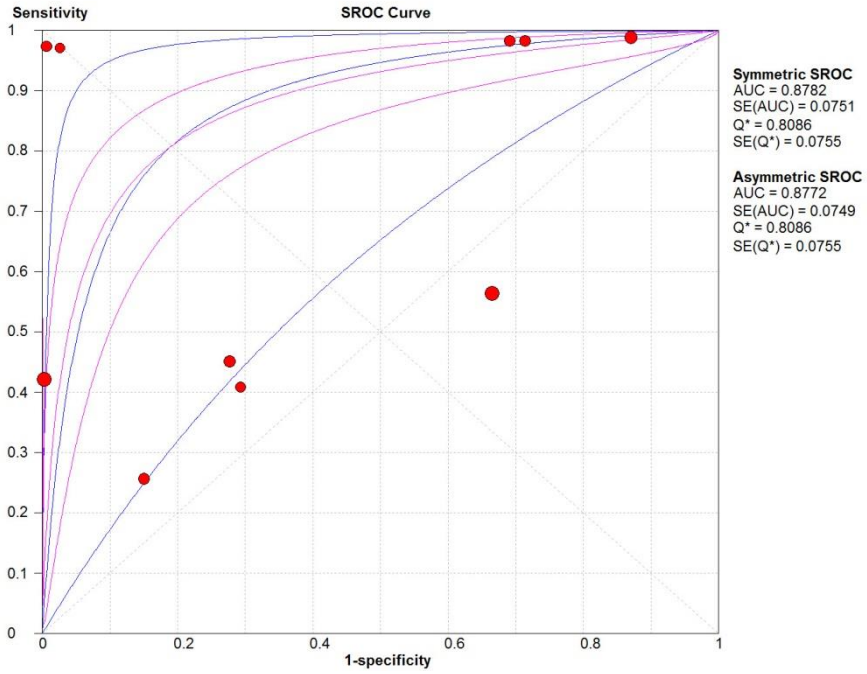
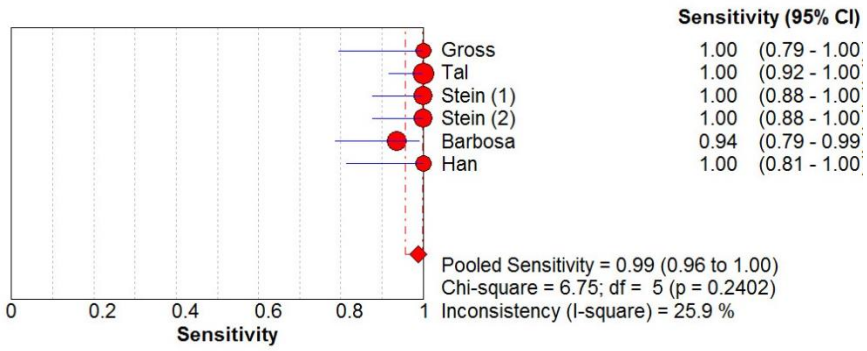
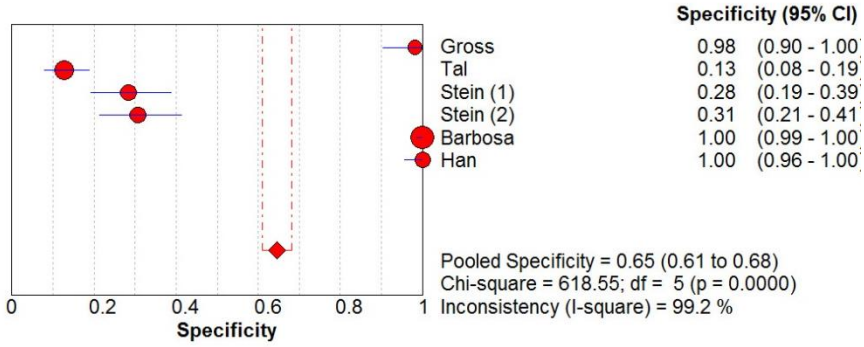

Sensitivity
SROC Curve
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Symmetric SROC
AUC = 0.8782
SE(AUC) = 0.0751
Q* = 0.8086
SE(Q*) = 0.0755
Asymmetric SROC
AUC = 0.8772
SE(AUC) = 0.0749
Q* = 0.8086
SE(Q*) = 0.0755

Figure 4.3: Pooled measures of diagnostic accuracy of SBI for ***active bleeding***. (a) sensitivity; (b) specificity; (c) SROC curve

(a)



(b)



(c)

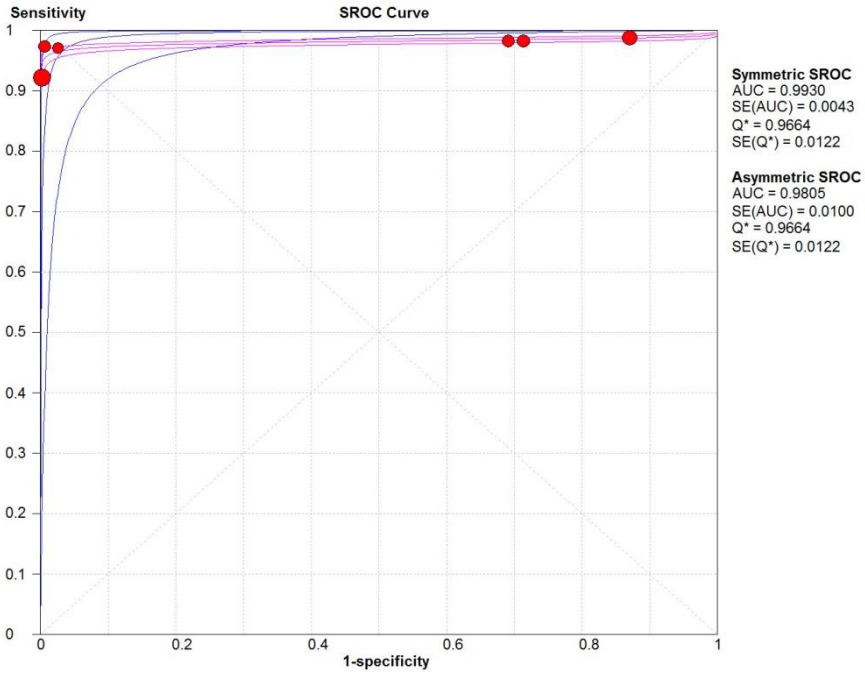
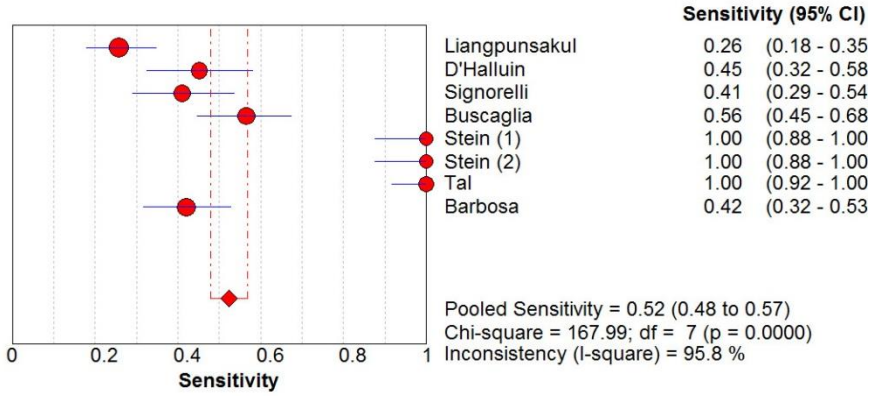
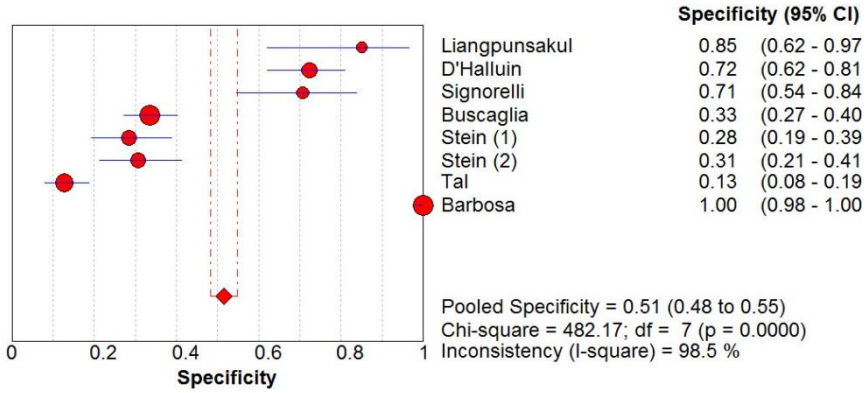


Figure 4.4: Pooled measures of diagnostic accuracy of SBI, taking into account only studies deemed moderate- to high-quality on QUADAS-2 analysis. (a) sensitivity; (b) specificity; (c) SROC curve

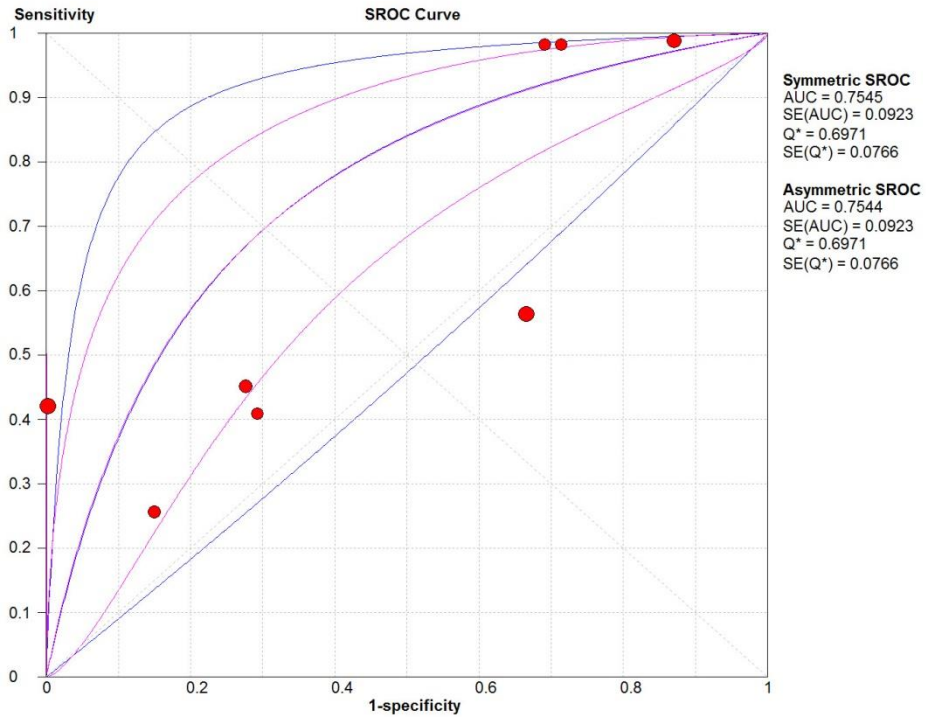
(a)



(b)



(c)


Sensitivity
SROC Curve
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Symmetric SROC
AUC = 0.7545
SE(AUC) = 0.0923
Q* = 0.6971
SE(Q*) = 0.0766
Asymmetric SROC
AUC = 0.7544
SE(AUC) = 0.0923
Q* = 0.6971
SE(Q*) = 0.0766

4.4 Discussion

4.4.1 Application of SBI in current clinical practice

Overall, the SBI software displayed poor to moderate sensitivity (55.3%) and specificity (57.8%) in detecting small bowel pathology with bleeding potential. However, SBI showed high sensitivity (98.8%) for active bleeding alone although its specificity remained low at 64.6% even in this clinical scenario. As mentioned previously, there have been studies investigating the effects of using CE earlier in the clinical assessment of suspected GI bleeding[11,124,125]. Although real-time viewers are now integrated into the majority of CE hardware, the images obtained still require reader interpretation[126]. Therefore, the use of artificial intelligence in CE reading is an attractive concept which has been gaining ground steadily[61,62,127]. Indeed, the sensitivity of SBI for active bleeding could further support the use of CE in the acute setting. For example, studies have shown that emergency physicians can perform CE reading for acute GI bleeding with minimal prior training[128,129]; the use of SBI can speed up this process. In this context, a robust SBI tool in conjunction with automated reading will allow for better clinical outcomes as highly-qualified clinical staff can be diverted to more skill-demanding tasks such as therapy of bleeding[130].

Furthermore, this meta-analysis highlights current technological limitations of using image-processing methods to aid CE reading. The SBI tool processes images based on wavelength and colour contrast. Interestingly, Park et al[112] conducted an experiment using SBI to detect simulated lesions against various coloured backgrounds. The SBI performed better with red lesions on a pale background, i.e. in frames with higher colour contrast. Similar results have been demonstrated in studies of other image enhancement software e.g. FICE or blue mode[55,131]. One plausible explanation for the overall moderate performance of the SBI software is that not all bleeding lesions are bright red or contrast strongly with bowel mucosa. Moreover, the size of a lesion and hence the number of red pixels in a frame does not always correlate with bleeding potential[97]. A combination of CE reading software aids could be a viable method for improving detection and shortening reading times, e.g. a combination of QuickView® and SBI as suggested by some of the included paper.

4.4.2 Limitations

Limitations of this review and meta-analysis include the marked heterogeneity of the included studies. Most studies reported accuracy parameters using the number of studies with any agreement between SBI and readers, rather than the agreement per lesion/area identified by the SBI. This is potentially misleading as the criteria for "true positives" in these cases was for a video to have one area flagged by SBI which was also determined by readers to have blood/a lesion. Therefore these videos could still contain other missed lesions. There was also limited information on review conditions used by the readers, such as speed of review and version of software. Most of the studies which did report capsule model used the M2A® capsule which is now superseded by newer versions; additional sensitivity analysis showed lower sensitivity in the studies which used M2A®. The analysis was further hampered by large amounts of missing information as several of the studies were abstracts. Finally, it was often unclear how a positive SBI finding was defined. Some studies defined a positive SBI as a specified number of flagged frames but others did not include this information.

4.5 Conclusion

The meta-analysis results show that the current SBI tool has limited validity in CE reading. However in the clinical context of active GI bleeding, it has good sensitivity, therefore supporting its use in the acute setting in patients with ongoing GI bleeding.

Chapter 5 Systematic Review and Meta-analysis: use of laxative bowel preparation in CE

In this third meta-analysis, I move on to clinical methods of image enhancement in CE. As previously discussed, the effectiveness of simethicone in reducing bubbles and therefore improving visualisation of the bowel lumen has already been established. This chapter therefore aims to investigate the effectiveness and clinical utility of laxative bowel preparation for CE.

5.1 Introduction: Role of laxatives in CE

The optimal pre-CE bowel preparation is a much-debated topic amongst CE users worldwide. Several regimes have been proposed with different laxatives, dosages and administration timing. Those in favor argue that laxatives improve image quality and SB mucosal visualization, therefore potentially increasing diagnostic yield[65,66]. Conversely, those advocating a clear liquid diet and pre-procedural overnight fast believe that this achieves adequate visualization with superior patient comfort and acceptability[67]. Despite several clinical studies and a few meta-analyses[68–71,132], the role of pre-procedural bowel purge remains controversial as no official societal guidelines exist[133].

Since the previous meta-analyses have been published, several more articles with contradictory messages have entered the literature. In this analysis I aimed to explore the effects of bowel preparation in SBCE by analyzing several parameters and outcomes of SBCE examination as per previous meta-analyses[68–71]. The primary outcome analysed is diagnostic yield for any findings and also clinically significant findings; secondary outcomes are SB visualization quality (SBVQ) and completion rate (CR).

5.2 Methods

5.2.1 Study selection

A comprehensive literature search of PubMed, Medline and Embase was conducted, through to September 2016, in order to identify relevant articles. The search terms used were "capsule endoscopy" (as keyword and MeSH term) *AND* ["preparation", "bowel preparation", "purgatives", "laxatives", "(preparation *OR* purge)", "cleansing" *OR* "prokinetics"], capturing studies from January 2000 to September 2016. Potentially relevant studies were initially identified by title and abstract; full texts were retrieved for detailed review and inclusion/exclusion criteria were applied. Further manual reference searches were conducted from the reference lists of review articles, editorials and previous meta-analyses, as well as those of all retrieved papers. Data were extracted independently by myself and a second reviewer. Disagreements and discrepancies were settled by a consensus opinion of three senior reviewers, experts in the subject matter, who were consulted when necessary.

Articles were included based on the criteria: (i) Published as full papers only, (ii) In English, (iii) Observational and interventional studies, (iv) On the use of laxatives in SBCE (whether compared with no laxatives or not), (v) Measuring the parameters of diagnostic yield for any findings and/or significant findings, SBVQ, CR, (vi) Adult patients only.

Studies not meeting these criteria were excluded. Additional exclusion criteria were: (i) Small sample size (n<10), (ii) Conference abstracts, letters, editorials, reviews, and meta-analyses, (iii) Insufficient data for meta-analysis and/or duplicate publications.

This study adhered to the PRISMA checklist (http://www.prisma-statement.org) as a standard.

5.2.2 Outcome measures

The primary outcome was ***diagnostic yield*** **(**abbreviated for this chapter as **"DY")**: any findings seen on SBCE including those "possibly" the cause of the patient's presentation, with a further subgroup of "definitely" significant findings, as defined by authors of the original articles.

Secondary outcomes were:

Small bowel visualization quality **(SBVQ)**: as defined by authors of included studies; if not, only "good" and "excellent" ratings were considered adequate. Studies which reported results as an average of visual rating, scores, without breakdown of results into adequate/inadequate numbers, were excluded from meta-analysis. When authors reported SBVQ per SB segment (i.e. proximal, middle, distal) we considered SBVQ adequate only when rated "good/excellent" in all segments.

Completion rate **(CR)**: number of SBCE examinations where the caecum was visualised, a consistent definition across all articles.

5.2.3 Statistical analysis

From the data extracted, pooled odds ratios (ORs) and proportions, with 95%CIs, were obtained for the outcomes (i) DY for all findings and significant findings; (ii) SBVQ and (iii) CR. The fixed effects model was used unless significant heterogeneity was present, where the random effects model was applied. For the outcome SBVQ, the number needed to treat (NNT) was estimated as the inverse of pooled risk differences[134,135]. Meta-analysis was conducted using the "meta" and "metafor" packages[136,137] in R statistical software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

In the presence of significant statistical heterogeneity, sensitivity analyses were conducted to evaluate the consistency of results. Outliers were identified and meta-analyses repeated without them to determine whether their exclusion significantly altered the magnitude or heterogeneity of the summary estimate. Further subgroup analyses were conducted to determine the potential effects of different study designs and populations: type of laxatives used, use of simethicone and/or prokinetics, timing of administration of laxatives, large

studies only (≥30 SBCEs in both laxative and control groups), high quality studies only as defined below, retrospective vs prospective study design (which also corresponded to cohort-based studies vs randomised controlled trials respectively).

Likelihood of publication bias was assessed with the construction of funnel plots, by plotting log ORs against precision (1/SE) of individual studies. Funnel plot symmetry was assessed using Egger's regression asymmetry test, and significant asymmetry was deemed present if $P<0.05$[138].

5.2.4 Quality assessment of included studies

Potential bias of the included studies was evaluated using the scoring system proposed by Rokkas *et al*[71], felt to be most specific to the topic of this meta-analysis. The items scored are as follows:

(1) Type of study: prospective (1 point) or retrospective/cohort study (0 points)
(2) Number of examiners: ≥2 (1 point) or only 1 (0 points)
(3) Blinding of examiners to preparation: yes (1 point) or no (0 points)
(4) Number of grades for overall bowel cleansing: ≥3 (1 point) or ≤2 (0 points)
(5) Whether the entire small bowel was evaluated: yes (1 point) or no (0 points)

Studies scoring 4/5 and above were considered to be high quality, studies scoring 2/5 and below as being at high risk of bias, and 3/5 as moderate risk of bias.

5.3 Results and meta-analysis

5.3.1 Study selection and included study characteristics

The initial search yielded 269 citations. Of those, 260 articles were found in PubMed; a subsequent Embase search found an additional 9 articles. These results were corroborated using Medline. On title and abstract review alone, 188 articles were excluded as non-relevant. Therefore, 81 articles proceeded to full text review. The detailed flow chart describing the process is presented in **Figure 5.1**.

The 40 studies that were eligible for final analysis were published from 2004-2016[139,140,149–158,141,159–168,142,169–178,143–148]. Out of these, 32 studies compared the use of laxatives against a control group who did not receive laxatives[139,140,149–152,155–159,161,141,162–168,171,174,175,142,176,178,143–148]; 8 studies examined only patients given laxatives (i.e. comparing one type of laxatives against another/ one regimen against another)[153,154,160,169,170,172,173,177]. Detailed study characteristics are shown in **Table 5.1**.

In total, 4380 patients received laxatives, while 2185 patients did not receive laxatives prior to SBCE. Polyethylene glycol (PEG) was used in 32 studies (3402 patients)[139,141,154,156–160,162–165,142,167–176,143,177,178,144,146–148,151,153]; sodium phosphate (NaP) in 11 studies (553 patients)[150,157,160164,171139,140,144–146,149]; 3 studies (134 patients) used Magnesium Citrate (MgC)[152,155,166]; another 3 studies (118 patients) used sodium picosulphate with MgC[173,175,178]. One study with 146 patients used mannitol[161].

Figure 5.1: Study selection for studies examining the use of laxative bowel preparation in CE

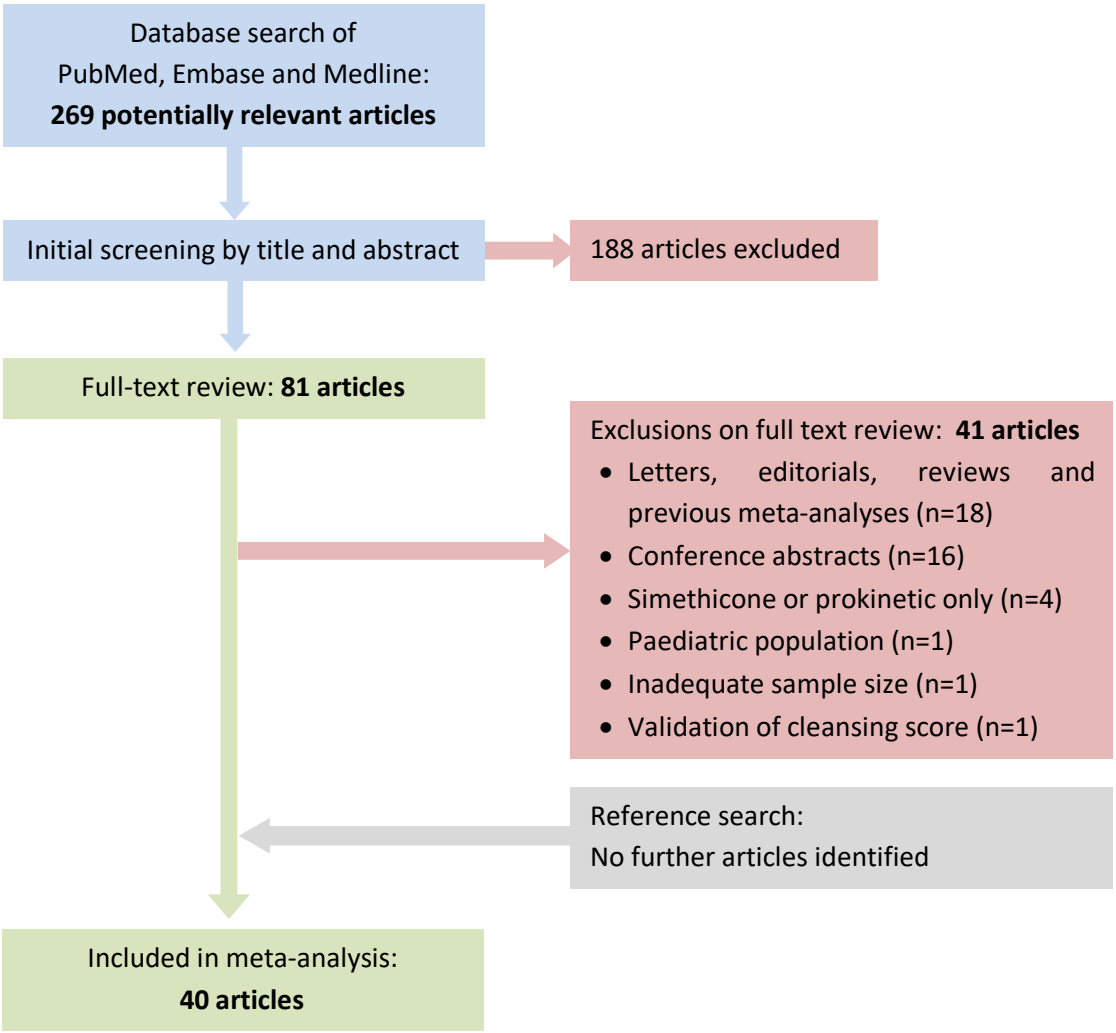


Table 5.1: Summary of studies examining the use of laxative bowel preparation in CE

Authors, Year (ref)	Country	Single / Multi-centre	Study Design*	CE model	Pt allocation	Reviewers	Types of bowel prep	Prokinetics or Simethicone	Pts given laxatives	Controls (no laxatives)	Type of Control	SBVQ scoring system based on**	DY definition	Overall risk of bias
Fireman, 2004[139]	Israel	Single	Retro	M2A®	-	2, blinded	PEG NaP	None	22 (PEG: 9, NaP: 13)	40	12h fast	-	Pathological findings	High
Niv, 2004 [140]	Israel	Single	Retro	Ns	-	2, blinded	NaP	None	22	10	8h fast	% time	-	Moderate
Viazis, 2004 [141]	Greece	Single	Prosp	M2A®	Randomised	3, blinded	PEG	None	40	40	Overnight fast	% of time and % mucosa visibility	Positive and suspicious findings	Moderate
Ben-Soussan, 2005 [142]	France	Single	Retro	M2A®	-	1, blinded	PEG	None	26	16	12h fast	Rating	Potentially bleeding lesions	High
Dai, 2005 [143]	Switzerland	Multi	Prosp	M2A®	By centre	3, blinded	PEG	None	33	29	12h fast	Amount of debris and % mucosa visibility	-	Low
Fireman, 2005 [144]	Israel	Single	Retro	M2A®	-	1, blinded	PEG NaP	None	26	40	12h fast	% mucosa visibility	-	High
Niv, 2005 [145]	Multicentre, international	Multi	Retro	Ns	By centre	1, blinded	NaP	None	23	23	Overnight fast	% time	Any lesions	High
Kalantzis, 2007 [146]	Greece	Multi	Retro	PillCam® SB	-	2, blinded	PEG NaP	None	119 (PEG: 65, NaP: 54)	67	8h fast	Rating	-	Moderate
Van Tuyl, 2007 [147]	The Netherlands	Single	Prosp	M2A®	Randomised	2, blinded	PEG	None	60	30	Overnight fast	% mucosa visibility	Definite and probable diagnoses	Moderate

Endo, 2008 [148]	Japan	Single	Prosp	PillCam® SB	Timing (initial group vs subsequent group)	2, blinded	PEG	None	27	32	12h fast	% mucosa visibility	Pathological findings	Low
Franke, 2008 [149]	The Netherlands	Single	Prosp	Ns	Randomised	3, blinded	NaP with bisacodyl	None	26	26	Overnight fast	Rating, multiple parameters	-	Low
Lapalus, 2008 [150]	France	Multi	Prosp	PillCam® SB	Randomised	2, blinded	NaP	None	63	64	8h fast	Amount of debris and % mucosa visibility	Saurin Score	Low
Wei, 2008 [151]	China	Single	Prosp	M2A®	Randomised	1, blinded	PEG	Simethicone (some pts)	60	30	12h fast + 1L clear fluids	% of time and % mucosa visibility	-	Low
Esaki, 2009 [152]	Japan	Single	Retro	M2A®, PillCam® SB	-	1	MgC	Simethicone (some pts)	36	39	12h fast	% mucosa visibility, multiple parameters	Any lesions	High
Fang, 2009 [153]	China	Single	Prosp	M2A®	Randomised	Ns	PEG	Simethicone (some pts)	64	-	-	% bubbles	-	High
Kantianis, 2009 [154]	Greece	Single	Prosp	M2A®	Randomised	1, blinded	PEG	None	201	-	-	% mucosa visibility	Any lesions and final diagnosis	Moderate
Postgate, 2009 [155]	UK	Single	Prosp	PillCam® SB	Randomised	1, blinded	MgC with senna	Metoclopramide (some pts)	76	74	Overnight fast	% mucosa visibility	Any lesions and lesions relevant to indication	Moderate
Rey, 2009 [156]	Multicentre, international	Multi	Prosp	Olympus Endocapsule	Randomised	Ns	PEG	Metoclopramide	57	59	Overnight fast	Rating, multiple parameters	-	Moderate

Wi, 2009 [157]	South Korea	Multi	Prosp	M2A®	Randomised	2 or more, blinded	PEG NaP	None	90 (PEG: 45, NaP: 45)	44	Overnight fast + 2L clear fluids	Adequate/ inadequate	Positive and suspicious findings	Moderate
Nouda, 2010 [158]	Japan	Single	Prosp	PillCam® SB	Randomised	4, blinded	PEG	Dimethylpolysiloxane	20	20	Overnight fast	Rating, %debris and bubbles	-	Low
Spada, 2010 [159]	Italy	Single	Prosp	PillCam® SB	Randomised	3, blinded	PEG	None	30	30	Overnight fast + low fibre diet before SBCE	% of time and % mucosa visibility	Diagnostic and suspicious findings	Low
Triantafyllou, 2010 [160]	Greece	Multi	Prosp	PillCam® SB	By centre	2, blinded	PEG NaP	None	95 (PEG: 48, NaP: 47)	-	-	Rating and % time	Positive and suspicious findings	Low
Chen, 2011 [161]	China	Single	Prosp	OMOM	Randomised	2, blinded	Mannitol	Simethicone (some pts)	146	47	Overnight fast	% mucosa visibility and % of frames, computer-aided calculation of % mucosa visibility	Any findings	Low
Hosono, 2011 [162]	Japan	Single	Prosp	PillCam® SB/ SB2	Randomised	2, blinded	PEG	Metoclopramide	40	40	12h fast	% of frames	Angioectasias, ulcers, erosions, tumours/polyps	Low
Park, 2011 [163]	South Korea	Single	Prosp	Ns	Randomised	Ns	PEG	None	45	23	12h fast	% of time and % mucosa visibility	Positive and suspicious findings	High

Pons Beltran, 2011 [164]	Spain	Multi	Prosp	M2A®	Randomised	1, blinded	PEG NaP	None	181 (PEG: 92, NaP: 89)	92	8h fast + 4L clear fluids	Rating	-	Moderate
Ito, 2012 [165]	Japan	Single	Prosp	PillCam® SB	Randomised	ns	PEG	Simethcone	20	22	12h fast	% mucosa visibility	-	Moderate
Ninomiya, 2012 [166]	Japan	Single	Prosp	PillCam® SB	Randomised	1, blinded	MgC	None	22	22	Overnight fast	Rating, multiple parameters	Any findings	Moderate
Niv, 2013 [167]	Israel	Multi	Prosp	PillCam® SB2	Randomised	1, blinded	PEG	None	50	148	Overnight fast (45), fast + low fibre diet (81), Ensure diet (22)	% mucosa visibility	Final diagnosis	Low
Rosa, 2013 [168]	Portugal	Single	Prosp	PillCam® SB2	Randomised	2, blinded	PEG	Simethicone (some pts)	37	20	Overnight fast	% mucosa visibility	Haemorrhagic lesions, LS >135	Low
Kim, 2014 [169]	South Korea	Single	Prosp	PillCam® SB2	Not randomised	1, blinded	PEG with or without coffee enema	None	34	-	-	% mucosa visibility and fluid transparency rating	Positive findings	Moderate
Black, 2015 [170]	USA	Single	Prosp	PillCam® SB	Randomised	1, blinded	PEG	Simethicone	34	-	-	Rating, multiple parameters	Saurin Score	Moderate
Lim, 2015 [171]	South Korea	Multi	Retro	PillCam®, Mirocam, Endocapsule	-	As per individual ctrs, not blinded	PEG NaP	None	1735 (PEG: 1564, NaP: 171)	425	ns	% mucosa visibility	-	High
Papamichael, 2015 [172]	Greece	Single	Prosp	PillCam® SB	Ns	Ns	PEG	Simethicone (some pts)	115	-	-	Rating of bubbles	Findings of clinical significance	Low

													and any findings	
Adler, 2016 [173]	Israel	Single	Prosp	PillCam® SB3	Randomised	1, blinded	PEG, Picosulphate + MgC	None	40 (PEG: 22, Picosulphate + MgC: 18)	-	-	Rating	Diagnostic findings and any findings	Low
Catalano, 2016 [174]	USA	Single	Retro	Ns	-	1, blinded	PEG	Simethicone	40	36	8h fast	% mucosa visibility and fluid transparency rating	-	High
Hookey, 2016 [175]	Canada	Single	Prosp	Ns	Randomised	3, blinded	PEG, Picosulphate + MgC	Simethicone	123 (PEG: 60, Picosulphate + MgC: 63)	59	Fluids only 36h before SBCE, overnight fast	% mucosal visibility. Computer scoring system as per Van Weyenberg *et al*, 2011.	-	Low
Klein, 2016 [176]	Israel	Multi	Retro	PillCam® SB/SB2	-	ns	PEG	None	360	500	Fluids only 24h before SBCE, 12h fast	Adequate/ inadequate	-	High
Magalhaes-Costa, 2016 [177]	Portugal	Single	Prosp	PillCam® SB3	Randomised	4, blinded	PEG	Simethicone	57	-	-	Rating, multiple parameters as per Brotz *et al*, 2009.	Clinically relevant lesions and any findings	Low
Rayner-Hartley, 2016 [178]	Canada	Single	Retro	Olympus Endocapsule	-	2, blinded (DY) and	PEG, Picosulp	None	85 (PEG: 48, Picosulph	38	Fluids only 36h before	% mucosa visibility	Abnormal study	Low

						1, blinded (SBVQ)	hate + MgC		ate + MgC: 37)		SBCE, overnight fast			

Abbreviations: DY diagnostic yield, LS Lewis Score, MgC magnesium citrate, NaP sodium phosphate, ns not specified, PEG polyethylene glycol, pts patients, SBVQ small bowel visualisation quality

*Study design: Prosp. prospective, Retro. retrospective

**SBVQ: “rating” refers to subjective grading systems based on “excellent”, “good”, “fair” and “poor” categories or similar. “% mucosa visibility” refers to systems based on the amount of small bowel mucosa visualised, either in frames or as a whole. “% time” refers to systems based on the amount of time (as a proportion of the small bowel examination time) that good mucosal visualisation was achieved.

5.3.2 Quality assessment of included studies

This is detailed in **Table 5.2**.

Table 5.2: Quality assessment of included studies

Authors, Year (ref)	Type of study: Prospective (1 pt) Retrospective /Cohort (0 pt)	No. of CE readers: ≥2 (1 pt) 1 (0 pt)	Blinding of readers: Yes (1 pt) No (0 pt)	No. of grades for overall bowel cleansing: ≥3 (1 pt) ≤2 (0 pt)	Evaluation of entire SB in all CEs: Yes (1 pt) No (0 pt)	Overall Score (max 5)	Overall risk of bias
Fireman, 2004 [139]	0	1	1	0	0	2	High
Niv, 2004 [140]	0	1	1	1	0	3	Moderate
Viazis, 2004 [141]	1	1	1	0	0	3	Moderate
Ben-Soussan, 2005 [142]	0	0	1	1	0	2	High
Dai, 2005 [143]	1	1	1	1	0	4	Low
Fireman, 2005 [144]	0	0	1	1	0	2	High
Niv, 2005 [145]	0	0	1	1	0	2	High
Kalantzis, 2007 [146]	0	1	1	1	0	3	Moderate
van Tuyl, 2007 [147]	1	1	1	0	0	3	Moderate
Endo, 2008 [148]	1	1	1	1	0	4	Low
Franke, 2008 [149]	1	1	1	1	1	5	Low
Lapalus, 2008 [150]	1	1	1	1	0	4	Low
Wei, 2008 [151]	1	0	1	1	1	4	Low
Esaki, 2009 [152]	0	0	0	1	0	1	High
Fang, 2009 [153]	1	0	0	1	0	2	High
Kantianis, 2009 [154]	1	0	1	1	0	3	Moderate
Postgate, 2009 [155]	1	0	1	1	0	3	Moderate
Rey, 2009 [156]	1	0	0	1	1	3	Moderate
Wi, 2009 [157]	1	1	1	0	0	3	Moderate
Nouda, 2010 [158]	1	1	1	1	0	4	Low
Spada, 2010 [159]	1	1	1	1	0	4	Low
Triantafyllou, 2010 [160]	1	1	1	1	0	4	Low
Chen, 2011 [161]	1	1	1	1	1	5	Low
Hosono, 2011 [162]	1	1	1	1	0	4	Low
Park, 2011 [163]	1	0	0	1	0	2	High
Pons Beltran, 2011 [164]	1	0	1	1	0	3	Moderate
Ito, 2012 [165]	1	0	1	1	0	3	Moderate
Ninomiya, 2012 [166]	1	0	1	1	0	3	Moderate
Niv, 2013 [167]	1	1	1	1	0	4	Low
Rosa, 2013 [168]	1	1	1	1	0	4	Low
Kim, 2014 [169]	1	0	1	1	0	3	Moderate
Black, 2015 [170]	1	0	1	1	0	3	Moderate
Lim, 2015 [171]	0	1	0	1	0	2	High
Papamichael, 2015 [172]	1	1	1	1	0	4	Low

Adler, 2016 [173]	1	0	1	1	1	4	Low
Catalano, 2016 [174]	0	0	1	1	0	2	High
Hookey, 2016 [175]	1	1	1	1	0	4	Low
Klein, 2016 [176]	0	0	0	0	0	0	High
Magalhaes-Costa, 2016 [177]	1	1	1	1	1	5	Low
Rayner-Hartley, 2016 [178]	0	1	1	1	1	4	Low

Abbreviations: CE capsule endoscopy; pt point; SB small bowel

5.3.3 Meta-analysis

A summary of meta-analysis results is shown in **Table 5.3(a)** (pooled proportions) and **Table 5.3(b)** (pooled ORs).

Table 5.3: Summary of meta-analysis results

Table 5.3(a): Meta-analyses of pooled proportions

Outcome/ Subgroup	No. of studies	No. of patients	Pooled proportion (%)	95%CI (%)	I^2 (%) (heterogeneity)	*p*-value for heterogeneity
DY for all SB findings						
ALL LAXATIVES	26	1816	58	52-64	80.9	<0.0001
No laxatives	20	1235	52	46-58	70.2	<0.0001
PEG	20	1294	58	52-63	72.1	<0.0001
PEG given before SBCE only	17	1218	56	50-62	69.7	<0.0001
NaP	6	213	68	49-82	80.6	<0.0001
NaP given before SBCE only	5	200	74	59-85	74.4	0.004
DY for significant SB findings						
ALL LAXATIVES	19	1584	45	39-52	82.7	<0.0001
No laxatives	13	1033	42	33-51	84.6	<0.0001
PEG	16	1189	45	38-52	79.9	<0.0001
PEG given before SBCE only	15	1162	43	36-50	77.7	<0.0001
NaP	3	155	60	43-75	75.6	0.02
NaP given before SBCE only	3	155	60	43-75	75.6	0.02
SBVQ (proportion of studies where adequate visualisation was achieved)						
ALL LAXATIVES	16	2979	68	59-76	91.5	<0.0001
No laxatives	12	1318	53	37-68	93.7	<0.0001
PEG	14	2557	64	52-74	92.3	<0.0001
PEG given before SBCE only	11	909	64	48-78	92.8	<0.0001
NaP	6	404	76	66-84	72.4	0.0003
NaP given before SBCE only	5	233	72	65-77	55.3	0.06
CR						
ALL LAXATIVES	30	2159	84	81-87	66.6	<0.0001
No laxatives	25	1519	80	76-83	56.3	0.0003
PEG	26	1610	84	78-88	73.5	<0.0001
PEG given before SBCE only	20	1452	85	81-88	69.6	<0.0001
NaP	8	356	78	73-82	0	0.82
NaP given before SBCE only	7	343	78	73-82	0	0.90

Abbreviations: CI confidence interval, CR completion rate, DY diagnostic yield, NaP sodium phosphate, PEG polyethylene glycol, SB small bowel, SBCE small bowel capsule endoscopy, SBVQ small bowel visualisation quality

Table 5.3(b): Meta-analyses of pooled ORs

Outcome/ Subgroup	No. of studies	No. of patients given laxatives	No. of patients with no laxatives	Pooled OR of outcome in patients given laxatives vs those not given laxatives	95%CI	I^2 (%) (heterogeneity)	*p*-value for heterogeneity
DY for all SB findings							
ALL LAXATIVES	19	1139	1188	1.11	0.85-1.44	39.1	0.0418
PEG	13	808	956	0.90	0.74-1.10	27.6	0.1666
NaP	5	166	181	1.40	0.88-2.22	0	0.4882
Other laxatives	4	165	162	1.30	0.83-2.05	52.7	0.0959
Laxatives given before SBCE only	17	1077	1108	1.12	0.85-1.48	41.3	0.0389
With simethicone	5	201	203	1.25	0.83-1.89	46.3	0.1142
No simethicone	15	938	1005	0.95	0.78-1.14	35.1	0.0879
Low risk of bias only	7	317	327	0.95	0.68-1.32	38.3	0.1366
Large studies only	10	845	975	1.11	0.76-1.63	63.4	0.0035
DY for significant SB findings							
ALL LAXATIVES	12	904	987	1.10	0.76-1.60	60.2	0.0037
PEG	10	720	849	0.90	0.73-1.11	59.7	0.0079
NaP	Insufficient data for meta-analysis						
Other laxatives	3	184	182	1.51	0.83-2.96	52.0	0.1247
Laxatives given before SBCE only	Insufficient data for meta-analysis						
With simethicone	3	125	124	0.78	0.46-1.32	0	0.6368
No simethicone	10	779	883	1.19	0.76-1.87	66.0	0.0017
Low risk of bias only	5	207	260	0.83	0.42-1.63	58.0	0.0494
Large studies only	8	769	896	1.11	0.68-1.80	73.1	0.0005
SBVQ (studies where adequate visualisation was achieved)							
ALL LAXATIVES	13	2767	1354	1.60	1.08-2.36	64.9	0.0006
PEG	11	2363	1321	1.44	1.01-2.06	53.4	0.0181
NaP	6	404	657	2.10	1.03-4.29	77.1	0.0006
Other laxatives	Insufficient data for meta-analysis						
Laxatives given before SBCE only	10	948	838	1.83	1.07-3.12	71.8	0.0002
With simethicone	3	84	82	2.31	0.53-10.1	68.0	0.0439
No simethicone	12	2683	1318	1.53	1.04-2.25	62.8	0.0018
Low risk of bias only	Insufficient data for meta-analysis						
Large studies only*	8	2609	1259	1.30	0.88-1.92	61.2	0.0117
CR							
ALL LAXATIVES	24	1661	1498	1.30	0.95-1.78	45.3	0.0090
PEG	19	1154	1305	1.34	0.91-1.97	50.6	0.0061

NaP	7	309	340	0.83	0.45-1.51	54.2	0.0414
Other laxatives	4	198	193	1.21	0.67-2.16	0	0.5659
Laxatives given before SBCE only	21	1559	1382	1.26	0.90-1.76	48.6	0.0068
With simethicone	7	358	289	1.10	0.68-1.86	0	0.4624
No simethicone	19	1303	1259	1.31	0.90-1.91	52.3	0.0042
Low risk of bias only	10	535	481	1.33	0.93-1.91	26.4	0.2006
Large studies only	15	1417	1292	1.25	0.85-1.84	58.4	0.0023

Abbreviations: CI confidence interval, CR completion rate, DY diagnostic yield, NaP sodium phosphate, OR odds ratio, PEG polyethylene glycol, SB small bowel, SBCE small bowel capsule endoscopy, SBVQ small bowel visualisation quality

*Large studies are defined as studies with ≥30 patients in both laxative and control groups

(i) Overall use of laxatives vs no laxatives for bowel preparation

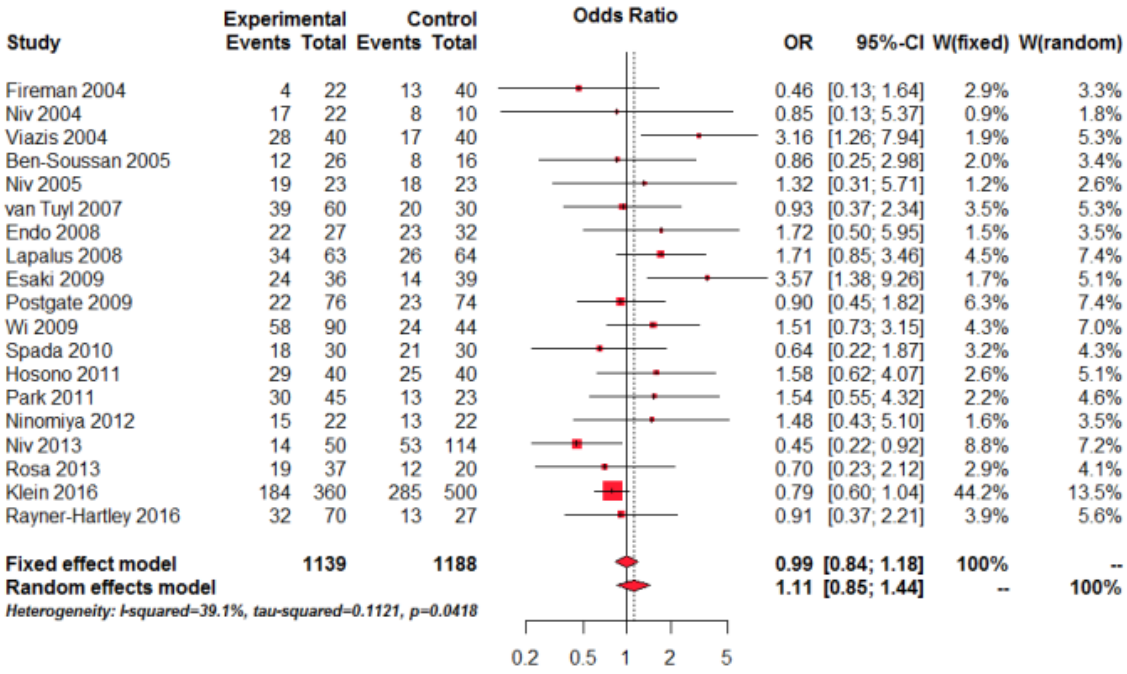
Primary outcomes: Diagnostic yield

DY (all SB findings): Overall, 26 studies (1816 patients)[139,140,155,157,159–163,166,167,169,141,170,172,173,176–178,142,145,147,148,150,152,154] were analyzed for the pooled proportion of SB findings. 58% of SBCE had SB findings (95%CI 52-64%; I^2=80.9, p<0.0001). 19 studies[139,140,157,159,162,163,166–168,176,178,141,142,145,147,148,150,152,155] examined DY of all findings in 1139 patients who received laxatives compared to those (1188 patients) who did not. In the group given laxatives, the OR for having any SBCE findings was 1.11 (95%CI 0.85-1.44; I^2=39.1%, p=0.04) **Figure 5.2**. The random effects model was used. There was no significant publication bias (Egger's test p=0.15).

DY (significant SB findings): Overall, 19 studies (1584 patients)[141,142,161,163,167,168,170,172,173,176,177,147,148,150,154,155,157,159,160] were analyzed for the pooled proportion of significant findings. 45% of SBCE had significant SB findings (95%CI 39-52%; I^2=82.7%, p<0.0001). 12 studies[141,142,168,176,147,148,150,155,157,159,163,167] examined the DY of significant findings in 904 patients who received laxatives, compared to 987 patients who did not receive laxatives. In patients given laxatives, the OR for SBCE with significant findings was 1.1 (95%CI 0.76-1.60; I^2=60.2%, p=0.004), **Figure 5.3**. The random effects model was used. There was no significant publication bias (Egger's test p=0.35).

Figure 5.2: Pooled OR of ***all SB findings*** when laxatives were used vs no laxatives. (a) Forest plot; (b) Funnel plot

(a)



(b)

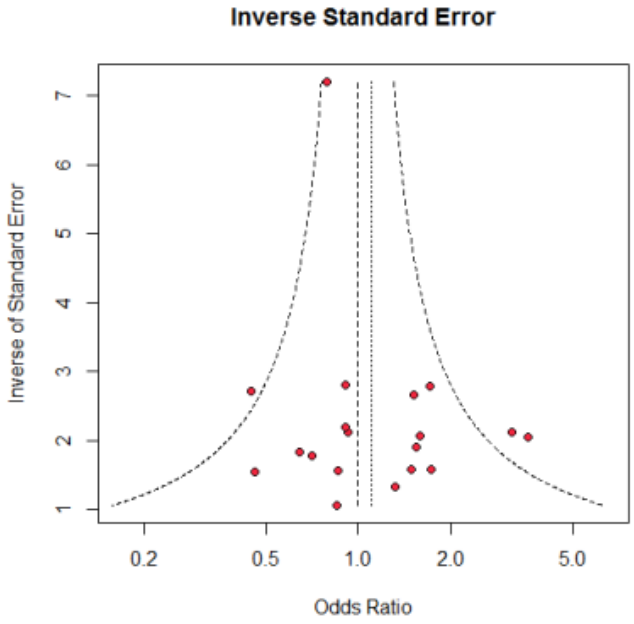
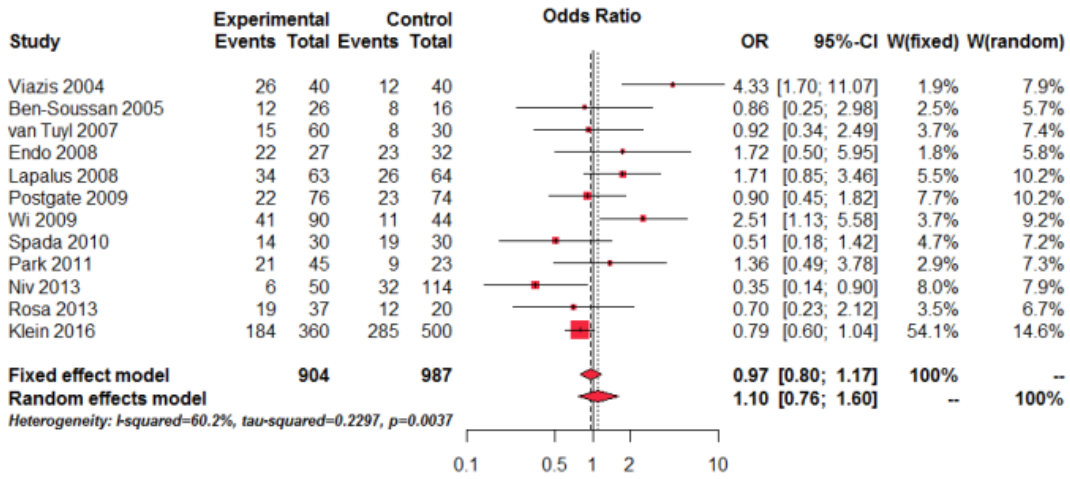
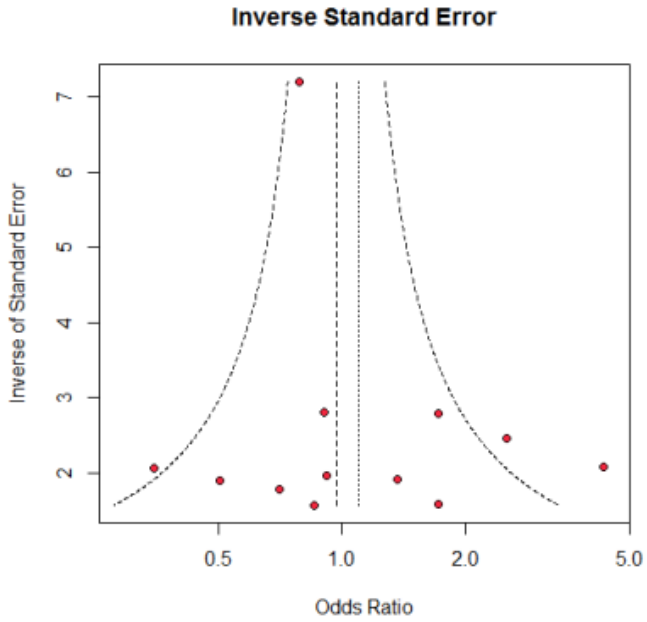


Figure 5.3: Pooled OR of ***significant SB findings*** when laxatives were used vs no laxatives. (a) Forest plot; (b) Funnel plot

(a)



(b)



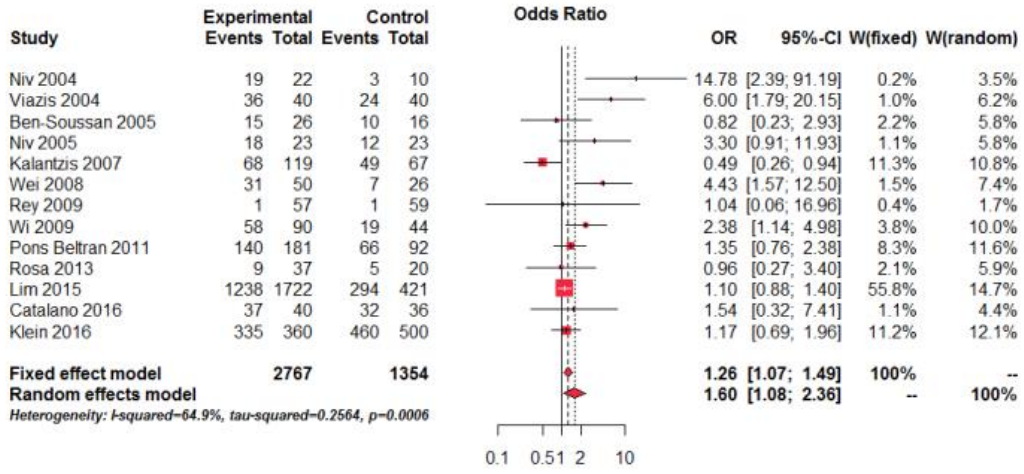
Secondary Outcomes

SBVQ: Overall, 16 studies (2979 patients) [140,141,171,172,174,176,177,142,145,146,151,156,157,164,168] were analysed for the pooled proportion of SBCE considered to have adequate visualization. Of those, 68% SBCE were considered to have adequate bowel preparation (95%CI 59-76%; I^2=91.5, p<0.0001). SBVQ with laxatives was examined in 13 studies (2767 patients)[140,141,171,174,176,142,145,146,151,156,157,164,168], as compared to SBVQ when no laxatives were used (n=1354). The OR of adequate SBVQ was 1.60 without laxatives compared to patients who received laxatives (95%CI 1.08-2.36; I^2=64.9%, p=0.0006), **Figure 5.4**. The random effects model was used; however no significant publication bias was found (Egger's test, p=0.103). The pooled risk difference was 0.07 (95% CI 0.01-0.13; I^2=74.4%, p<0.0001), giving a NNT of 14 (95%CI 8-68).

CR: Overall, 30 studies[139,140,154,155,157–160,162–165,141,166–170,172,174–176,178,142,145–148,150,151] with 2159 patients were analyzed for pooled SBCE CR. The overall CR was 84% (95%CI 81-87%; I^2=66.6%, p<0.0001). 24 studies[139,140,155,157–159,162–164,166–168,141,174–176,178,142,145–148,150,151] examined CR in 1661 patients who received laxatives compared to 1498 patients who were not given laxatives. The OR for completed SBCE examinations was 1.30 (95%CI 0.95-1.78; I^2=45.3%, p=0.009) between the two groups, **Figure 5.5**. The random effects model was used due to the significant heterogeneity. There was no significant publication bias (Egger's test, p=0.20).

Figure 5.4: Pooled OR of having ***improved SBVQ*** when laxatives were used vs no laxatives. (a) Forest plot; (b) Funnel plot

(a)



(b)

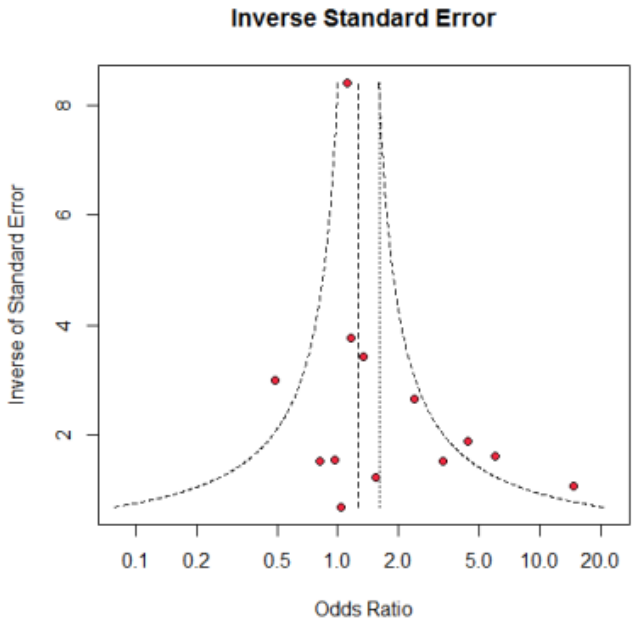
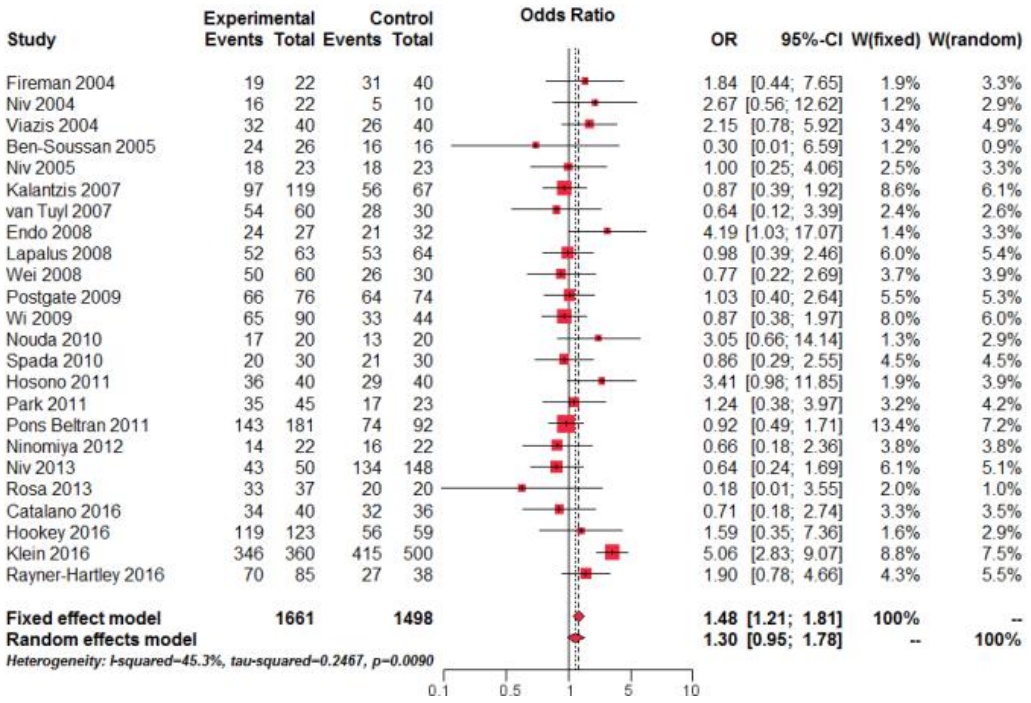
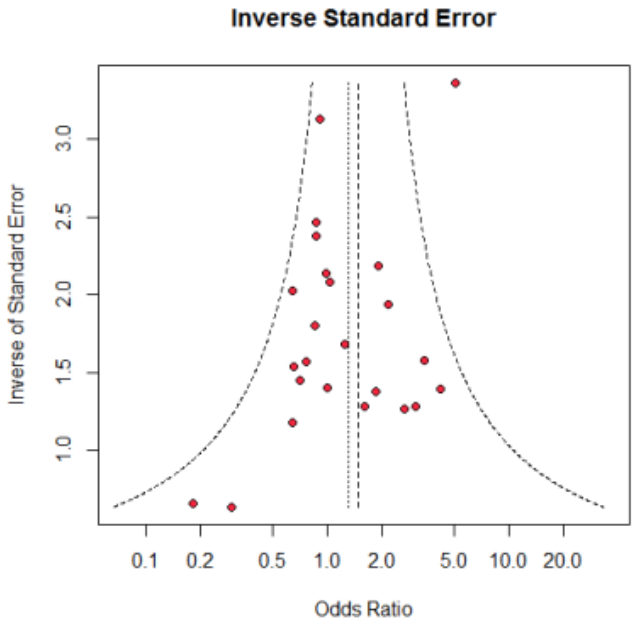


Figure 5.5: Pooled OR of ***completed SB examination*** when laxatives were used vs no laxatives. (a) Forest plot; (b) Funnel plot

(a)



(b)



(ii) PEG and NaP

DY: For patients given PEG, the pooled OR for all SB findings was 0.90 (95%CI 0.74-1.10; I^2=27.6%, *p*=0.17). The pooled OR for all findings in patients given NaP was 1.40 (95%CI 0.88-2.22; I^2=0%, *p*=0.49).

SBVQ: The OR of adequate visualisation in patients given PEG was 1.44 (95%CI 1.01-2.06; I^2=53.4%, *p*=0.02). The pooled risk difference was 0.02 (95%CI -0.04-0.08; I^2=71.2%, *p*=0.0001); NNT for PEG = 53 (95%CI -25-12).

Patients given NaP had an OR for adequate visualisation of 2.10 (95%CI 1.03-4.29; I^2=77.1%, *p*=0.0006). The pooled risk difference was 0.16 (95%CI 0.02-0.30; I^2=79.2%, p=0.0002); NNT for NaP = 7 (95%CI 4-50).

CR: The pooled OR for completion in patients given PEG was 1.34 (95%CI 0.91-1.97; I^2=50.6%, *p*=0.006), compared to a pooled OR of 0.83 (95%CI 0.45-1.51; I^2=54.2%, *p*=0.04) in patients given NaP.

Further subgroup analyses for the different PEG dosages, i.e. low volume (<2L PEG), 2L PEG and high volume (>2L PEG) are shown in **Table 5.4**.

Table 5.4: Subgroup analyses for different PEG dosing regimes

Table 5.4(a): Pooled proportions for different PEG doses

Outcome/ Subgroup	No. of studies	No. of patients	Pooled proportion (%)	95%CI (%)	I^2 (%) (heterogeneity)
DY for all SB findings					
2L PEG	16	1024	56	51-62	61.3
<2L PEG	4	136	67	52-79	64.4
>2L PEG	3	134	44	22-69	76.9
PEG given before CE	17	1218	56	50-62	69.7
With simethicone	6	235	63	56-69	41.1
No simethicone	16	1059	54	48-61	71.2
DY for significant SB findings					
2L PEG	15	1007	44	37-50	70.0
<2L PEG	Insufficient data for meta-analysis				
>2L PEG	Insufficient data for meta-analysis				
PEG given before CE	15	1162	43	36-50	77.7
With simethicone	5	195	48	41-55	52.6
No simethicone	13	994	43	35-52	82.0
SBVQ (proportion of studies where adequate visualisation was achieved)					
2L PEG	10	1883	64	50-76	93.3
<2L PEG	Insufficient data for meta-analysis				
>2L PEG	Insufficient data for meta-analysis				
PEG given before CE	11	909	64	48-78	93.3
With simethicone	5	197	72	51-86	83.2
No simethicone	12	2360	58	44-71	92.9
CR					
2L PEG	16	1077	85	80-90	72.9
<2L PEG	7	245	86	80-90	0
>2L PEG	4	226	79	73-84	0
PEG given before CE	20	1452	85	81-88	69.6
With simethicone	9	328	86	81-89	36.7
No simethicone	18	1240	85	80-88	66.6

Abbreviations: CE capsule endoscopy, CI confidence interval, CR completion rate, DY diagnostic yield, PEG polyethylene glycol, SB small bowel, SBVQ small bowel visualisation quality

Table 5.4(b): Pooled ORs for different PEG doses

Outcome/ Subgroup	No. of studies	No. of patients given laxatives	No. of patients with no laxatives	Pooled OR of outcome in patients given laxatives vs those not given laxatives	95%CI	I^2 (%) (heterogeneity)
DY for all SB findings						
2L PEG	9	638	817	0.84	0.68-1.04	38.4
<2L PEG	4	136	129	1.28	0.76-2.14	0
>2L PEG	Insufficient data for meta-analysis					
DY for significant SB findings						
2L PEG	9	638	817	1.01	0.63-1.63	62.2
<2L PEG	Insufficient data for meta-analysis					
>2L PEG	Insufficient data for meta-analysis					
SBVQ (proportion of studies where adequate visualisation was achieved)						
2L PEG	6	573	687	1.21	0.66-2.21	63.1
<2L PEG	Insufficient data for meta-analysis					
>2L PEG	Insufficient data for meta-analysis					
CR						
2L PEG	11	763	977	1.09	0.59-2.03	66.0
<2L PEG	6	225	190	2.03	1.21-3.40	0
>2L PEG	3	126	155	1.13	0.61-2.07	0

Abbreviations: CI confidence interval, CR completion rate, DY diagnostic yield, OR odds ratio, PEG polyethylene glycol, SB small bowel, SBVQ small bowel visualisation quality

(iii) Timing of laxative administration

There were insufficient data to carry out an analysis of studies where laxatives were given post-SBCE ingestion; therefore the group of patients where laxatives were given only before SBCE ingestion was meta-analysed.

DY: The pooled OR of having SB findings was 1.12 (95%CI 0.85-1.48; I^2=41.3%, p=0.04) in patients given laxatives only prior to SBCE. There was insufficient data for the meta-analysis of the OR of significant SB findings.

SBVQ: The pooled OR of adequate visualization in patients given laxatives before SBCE was 1.83 (95%CI 1.07-3.12; I^2=71.8%, p=0.0002).

CR: The pooled OR of completed SBCE examinations was 1.26 (95%CI 0.90-1.76; I^2=48.6%, p=0.007) in this group of patients.

5.3.4 Sensitivity analyses

Further sensitivity analyses were conducted and are detailed in **Table 5.5.** Please also see the appendices for a table detailing the studies included in each subgroup analysis.

Retrospective vs Prospective studies: The pooled ORs for the DYs of retrospective studies and prospective studies did not differ significantly when DY for all findings (p=0.13) and significant findings only (p=0.14) were examined. SBVQ also did not differ significantly between retrospective and prospective studies (p=0.13). There was a significant difference in pooled OR for completion between retrospective and prospective studies (p=0.001). Retrospective studies showed a higher pooled OR for completion; however moderate to high heterogeneity was seen in the group of retrospective studies despite methodical study exclusion, in contrast to the low heterogeneity in the prospective studies.

Use of simethicone: Pooled ORs for DY of both overall (p=0.21) and significant findings (p=0.23) did not differ significantly whether simethicone was used or not. There were also no significant subgroup differences with or without simethicone use for SBVQ (p=0.59) and CR (p=0.21).

Studies at low risk of bias vs studies at moderate-high risk of bias: When comparing studies at low risk of bias against those at moderate to high risk of bias, there were no significant subgroup differences for DY of all findings (p=0.74) and significant findings (p=0.29). SBVQ and CR also did not differ significantly between the subgroups (p=0.65 and p=0.50 respectively).

Large studies vs small studies: There was no significant difference in OR for DY overall (p=0.93) or for significant findings only (p=0.97). Furthermore, neither SBVQ nor CR differed significantly between the subgroups (p=0.19 and p=0.96 respectively). However it was noted that the large studies with 30 or more patients in both laxative and control groups showed greater heterogeneity compared to smaller studies.

Table 5.5: Summary of sensitivity analyses

Outcome/ Subgroup	No. of studies	No. of patients given laxatives	No. of patients with no laxatives	Pooled OR of outcome in patients given laxatives vs those not given laxatives	95%CI	I^2 (%) (heterogeneity)
1. Retrospective vs Prospective studies						
1.1 DY for all SB findings						
Retrospective	7	559	655	0.88	0.69-1.11	41
Prospective	12	580	533	1.15	0.89-1.47	35
Test for subgroup differences	Chi^2=2.35; p=0.13, I^2=57.4%					
1.2 DY for signficant SB findings						
Retrospective	2	386	516	0.79	0.61-1.03	0
Prospective	10	518	471	1.18	0.74-1.88	61
Test for subgroup differences	Chi^2=2.16; p=0.14, I^2=53.8%					
1.3 SBVQ						
Retrospective	7	2312	1073	1.23	0.75-2.02	65
Prospective	6	455	281	2.20	1.26-3.84	44
Test for subgroup differences	Chi^2=2.33; p=0.13, I^2=57.1%					
1.4 CR						
Retrospective	8	697	730	2.26	1.62-3.15	63
Prospective	16	964	768	1.11	0.85-1.44	1
Test for subgroup differences	Chi^2=10.91; p=0.001, I^2=90.8%					
2. Simethicone vs no simethicone						
2.1 DY for all SB findings						
Simethicone	5	201	203	1.25	0.83-1.89	46
No simethicone	15	938	1005	0.94	0.78-1.14	34
Test for subgroup differences	Chi^2=1.56; p=0.21, I^2=36.1%					
2.2 DY for significant SB findings						
Simethicone	3	125	124	0.78	0.46-1.32	0
No simethicone	10	779	883	1.19	0.76-1.87	66
Test for subgroup differences	Chi^2=1.45; p=0.23, I^2=31.0%					
2.3 SBVQ						
Simethicone	3	84	82	2.31	0.53-10.05	68
No simethicone	12	2683	1318	1.53	1.04-2.25	63
Test for subgroup differences	Chi^2=0.29; p=0.59, I^2=0%					
2.4 CR						
Simethicone	7	358	289	1.10	0.68-1.76	0
No simethicone	19	1303	1259	1.54	1.23-1.92	52
Test for subgroup differences	Chi^2=1.61; p=0.21, I^2=37.7%					

3. Low risk of bias vs mod-high risk of bias						
3.1 DY for all SB findings						
Low risk of bias	7	317	327	0.95	0.68-1.32	38
Mod-high risk of bias	12	822	861	1.01	0.83-1.24	44
Test for subgroup differences	Chi^2=0.11; p=0.74, I^2=0%					
3.2 DY for significant SB findings						
Low risk of bias	5	207	260	0.83	0.42-1.63	58
Mod-high risk of bias	7	697	727	1.31	0.80-2.15	67
Test for subgroup differences	Chi^2=1.14; p=0.29, I^2=12.2%					
3.3 SBVQ						
Low risk of bias	2	87	46	2.16	0.49-9.59	70
Mod-high risk of bias	11	2680	1308	1.50	1.00-2.25	65
Test for subgroup differences	Chi^2=0.21; p=0.65, I^2=0%					
3.4 CR						
Low risk of bias	10	535	481	1.33	0.93-1.91	26
Mod-high risk of bias	14	1126	1017	1.55	1.21-1.98	56
Test for subgroup differences	Chi^2=0.45; p=0.50, I^2=0%					
4. Large vs smaller studies						
4.1 DY for all SB findings						
Large studies	10	845	975	0.99	0.82-1.20	65
Smaller studies	9	294	213	1.01	0.68-1.49	0
Test for subgroup differences	Chi^2=0.01; p=0.93, I^2=0%					
4.2 DY for significant SB findings						
Large studies	8	769	896	1.11	0.68-1.80	73
Smaller studies	4	135	91	1.09	0.62-1.93	0
Test for subgroup differences	Chi^2=0.00; p=0.97, I^2=0%					
4.3 SBVQ						
Large studies	8	2609	1259	1.30	0.88-1.92	61
Smaller studies	5	158	95	2.56	1.01-6.48	61
Test for subgroup differences	Chi^2=1.74; p=0.19, I^2=42.7%					
4.4 CR						
Large studies	15	1426	1292	1.43	1.14-1.78	58
Smaller studies	9	244	206	1.41	0.88-2.26	6
Test for subgroup differences	Chi^2=0.00; p=0.96, I^2=0%					

Abbreviations: CI confidence interval, CR completion rate, DY diagnostic yield, OR odds ratio, PEG polyethylene glycol, SB small bowel, SBVQ small bowel visualisation quality

5.4 Discussion

To date, the ideal preparation for SBCE has been a matter of several meta-analyses and clinical trials with contradictory results. Bowel preparation with laxatives is often regarded the least tolerable part of the procedure, as repeatedly shown in colonoscopy studies[179,180]. The high PEG volume makes it difficult to ingest and can cause fluid overload in susceptible patients[181,182]. NaP has its own accompanying risks including hyperphosphataemia[183–185] and comes with warnings from several national drug regulatory authorities[186]. It would therefore be desirable to abandon laxatives in SBCE, especially if no adverse effect on DY can be confirmed. Therefore, the major questions regarding the use of bowel preparation in SBCE are: (a) Do laxatives improve DY and/or SBVQ; and (b) If laxatives are given, what is the optimal timing, i.e. before or after CE ingestion.

5.4.1 Whether laxatives improve DY and/or SBVQ

Due to the randomness of capsule movement in the gut, DY is largely dependent on the percentage of mucosa visualized as well as the clarity of the obtained images[66,133]. However, DY is also affected by many other factors such as patient case mix and thresholds for SBCE referral at different centers, in addition to the experience and reporting confidence of individual SBCE readers[187–189]. On the other hand, SBCE technology has now markedly improved and most commercially available capsules offer higher definition, increased frame-rate and a 12-hour recording time with real-time viewer capacity.

This analysis shows that the use of laxatives in SBCE did not significantly improve the detection of SB findings overall, nor significant SB findings, independent of type of laxatives used. The OR for SBCE DY (1.11) was lower in our meta-analysis compared to previous meta-analyses[68–71,132], likely due to the significantly larger size of this meta-analysis, **Table 5.6**. It was evident that there is still a lack of clear definition for DY in SBCE. Most of the included studies classified SBCE findings as “positive/definite/diagnostic” and “suspicious/probable cause of symptoms”; these classifications are inconsistent and/or not specified across studies. Attempts to standardize the reporting of SBCE findings[93,190–192] remain unvalidated and are not in common everyday use.

Table 5.6: Comparison of current meta-analysis results to those of previous meta-analyses

Authors, Year (ref)	Outcome measure	No. of studies	Laxatives/ No laxatives	Pooled OR (95%CI)
Niv, 2008 (7)	DY	-	-	-
	SBVQ	5	130/107	Results not reported as OR. Pooled proportion for adequate visualization: 78% in pts given laxatives vs 49% in pts not given laxatives.
Rokkas *et al*, 2009 (5)	DY	5	263/213	1.81 (1.25-2.63)
	SBVQ	7	404/249	2.11 (1.25-3.57)
Belsey *et al*, 2012 (2)	DY	5	Ns	1.88 (1.24-2.84)
	SBVQ	8	424/322	2.31 (1.46-3.63)
Song *et al*, 2013 (6) *PEG only	DY	5	145/148	1.97 (1.20-3.24)
	SBVQ	4	174/173	4.02 (0.71-8.24)
Kotwal *et al*, 2014 (4)	DY	PEG: 5 NaP: 3	PEG: 131/83 NaP: 106/80	PEG: 1.68 (1.16-2.42) NaP: 1.77 (1.18-2.64)
	SBVQ	PEG: 5 NaP: 2	PEG: 183/114 NaP: 101/85	PEG: 3.13 (1.70-5.75) NaP: 2.06 (0.74-5.70)
Present meta-analysis	DY	19	1139/1188	1.11 (0.85-1.44)
	SBVQ	13	2767/1354	1.60 (1.08-2.36)

Abbreviations: CI confidence interval, DY diagnostic yield, NaP sodium phosphate, ns not specified, OR odds ratio, PEG polyethylene glycol, SBVQ small bowel visualization quality

The use of SBVQ as an outcome measure is subject to the same limitations, as there remains no clear consensus on what constitutes "adequate" visualization quality. To circumvent this we applied stringent measures for determining SBVQ in studies where the exact definition of good visualization was not specified. For example, if a study reported results as ratings of "excellent", "good", "fair" and "poor" (or similar), only "excellent " and "good" ratings were considered adequate. Recently, Ponte et al[193] examined various SBVQ scales and concluded that where the entire SBCE video was examined results may be more consistent and accurate. They also suggested that computer-assisted grading scales[194,195], when adequately developed, are likely to be more objective than operator-dependent grading scales[196].

Despite its drawbacks, SBVQ remains a key quality indicator for SBCE, a purely image-based technique, regarded a surrogate marker of the reader's confidence in detecting and characterizing SB findings. SBVQ improved slightly in certain subgroups, namely studies with NaP, and simethicone alongside laxatives. Simethicone has previously been shown to

improve SBVQ[197,198]. Therefore, a NNT of 14 required to achieve adequate SBVQ in one additional patient suggests that there may be a possible benefit with laxatives that may have been underestimated due to the aforementioned sources of heterogeneity. Nevertheless, analyzing the effects of the 2 main subgroups of laxatives, the OR of NaP achieving adequate SBVQ was 2.01 (NNT=7), whereas PEG alone had a lower OR of 1.44 and much higher NNT of 53. The high NNT observed with PEG calls into question the utility of this preparation in the everyday clinical practice, at least with conventional administration schedules.

5.4.2 Whether laxatives should be given for SBCE examination

Interestingly, Adler et al[173] recently proposed that although fasting alone results in adequate proximal SB images; the distal SB is often less well prepared, a consistent finding from other studies. They found that post-SBCE Na picosulphate improved distal SB visualization compared to conventional 2L PEG ($p<0.0001$). Hence, they advocate the administration of laxatives post SBCE ingestion. The use of booster doses of laxatives post capsule ingestion in capsule colonoscopy has been shown to improve large bowel visualization[199,200].

At present, there is inadequate data to perform a subgroup analysis for laxative administration post-capsule ingestion. However, in order to gauge this, a subgroup analysis was carried out, examining only the studies where laxatives were given prior to SBCE. As this pooled OR for DY (1.12) is similar to that of the overall analysis of all laxatives and dose timings (1.11), it can be inferred that the studies where laxatives were given post-SBCE or in split doses before and after capsule ingestion did not make a great difference in DY. Nevertheless, further studies on this issue are certainly warranted.

A significant proportion of patients (10-20%) still have incomplete SBCE with potential impact on DY. Therefore the effect of laxatives on SBCE CR was also examined. These results show that the administration of laxatives did not impact on CR, regardless of the type of laxative, administration schedule or the dosage. However, this meta-analysis captured studies conducted over 12 years, and technological improvements, as well as differences between commercially available capsules, could have minimized the possible impact of laxatives on CR.

5.4.3 Cost-effectiveness

Any changes to patient preparation which increase cost-effectiveness without compromising quality of clinical investigation are desirable. Performing SBCE without the administration of bowel preparation could be advantageous not only for patients, but also for healthcare providers. Potential cost savings, based on the current edition of the British National Formulary (BNF)[201], for a center performing 100 capsules/year are reported in **Table 5.7**. Further cost savings could also result from avoiding pre-admission of certain patient groups, e.g. elderly patients with multiple comordibities, for bowel preparation. Recently, Triantafyllou et al[202] found that following implementation of austerity measures in Greece, the number of SBCEs performed decreased and indications were rationalized to maximize yield.

Table 5.7: Estimated costs of different types of laxatives

Laxative	Definition of 1 dose	Cost of 1 dose	Cost of 100 doses
PEG as Moviprep® (Norgine)	2 pairs of sachets in 2L water, either single or split dose	£9.87	£987.00
NaP as Fleet Phospho-soda® (Casen-Fleet)	2 x 45ml in split dose	£4.79	£479.00
Picosulphate with MgC as Picolax® (Ferring)	2 sachets in split dose	£3.39	£339.00

Abbreviations: MgC magnesium citrate, NaP sodium phosphate, PEG polyethylene glycol

5.4.4 Limitations

An important limitation of this meta-analysis is the statistical heterogeneity. An attempt was made to address this by performing subgroup analyses; however, the heterogeneity may also be due to the lack of standardized definitions for outcome measures, as previously discussed. Another significant cause of heterogeneity is the mix of study types including both prospective and retrospective studies, in the forms of randomised controlled trials and observational cohort studies. Due to lack of sufficient data, certain subgroups, including indications for SBCE or timing of laxative administration, could not be statistically analysed. Furthermore, the “control” group of patients who did not receive pre-SBCE laxatives included a range of fasting regimens, from liquid diets or a straightforward fast, to low-residue diets for a few days before SBCE.

5.5 Conclusion

This review and meta-analysis suggests that the use of laxatives did not significantly improve diagnostic yield or completion rate of SBCE, but did marginally increase SBVQ. Although no effect of laxatives on diagnostic yield was noted, the effect on SBVQ suggests that the use of laxatives in SBCE may be beneficial where there is increased likelihood of subtle findings such as mucosal aphthae and small growths. There is emerging anecdotal evidence, especially from the use of the colon capsule, that one or more additional doses of laxatives given after capsule ingestion can improve SBVQ and potentially diagnostic yield in the distal SB to colon. Based on this meta-analysis, there is limited evidence to support the use of laxatives in SBCE which remains fairly dependent on individual preference or local practices. In the process of this work, the need to develop standardized objective visualization scoring and recording of SBCE findings has also been demonstrated.

Chapter 6 Timing of CE in relation to diagnostic pathway for GI bleeding

The previous chapters have examined the data on various methods to improve image quality and bowel visualisation in CE. In this chapter, the focus now widens to ways in which we can utilise CE more effectively in the clinical setting, starting by examining how the timing of CE in the investigation pathway for patients with SBB can contribute to its diagnostic value, and to optimising both patient care and resource use.

6.1 Introduction

As an investigation for SBB, CE is usually performed non-acutely as an outpatient procedure; however as previously discussed, there is now evidence that performing CE closer to the index bleeding episode – ideally within the first 72h of presentation – increases its diagnostic yield[36]. This is corroborated by studies showing that for the same indications, inpatient CE has a higher diagnostic yield compared to outpatient procedures [37–39].

At present the role of CE in patients presenting acutely with suspected SBB is often as the "next-line" investigation following after negative bidirectional endoscopy. However, although the rationale for UGIE as a first-line investigation remains undisputed due to its ability to both diagnose and treat, performing colonoscopy in the acute setting is a demanding task both for the patient and clinician, and is often limited by the quality of bowel preparation and patient fitness or tolerance. Furthermore anecdotally it has been observed that the logistics of scheduling urgent inpatient colonoscopies often causes longer hospital stays. At our large tertiary care hospital, there has been a trend for performing CE following a negative index UGIE alone, with anecdotal evidence that by doing so unnecessary colonoscopies have been avoided in certain patients. Therefore, this study aimed to examine the effect of earlier investigation with CE for inpatients with suspected SBB manifesting as melaena or severe IDA. The primary outcome was to assess in patients with suspected SBB and negative initial UGIE, whether the use CE prior to inpatient colonoscopy reduced the subsequent need for urgent colonoscopic investigation and/or length of inpatient stay.

6.2 Methods

6.2.1 Patient selection

This was a retrospective study of all inpatient CEs carried out at our tertiary care academic centre from March 2005 to March 2017, using a prospectively-designed and continuously-maintained database. Data collected were:

- Patient demographics: age, gender
- Relevant past medical history: cardiovascular, liver and/or renal disease; use of antiplatelet and/or anticoagulant medications; any previous episodes of GI bleeding;
- Circumstances of admission;
- CE indications and findings;
- Timing of CE relative to admission and prior conventional endoscopies;
- Conventional endoscopies carried out within the past 6 months prior to admission;
- Further investigations and results;
- Patient outcomes, defining follow-up period as the date of last recorded patient contact with local healthcare services, discharge (back) to another health board, or death.

Inpatients undergoing CE for suspected SBB were included. Suspected SBB was defined as IDA or melaena in patients with negative UGIE, with no other signs or symptoms suggesting lower GI tract pathology such as frank rectal bleeding, diarrhoea with associated significant weight loss or lower abdominal pain. Over the study period, patients admitted with UGIE-negative IDA or melaena underwent CE either following nondiagnostic bidirectional endoscopy (referred to as "**Group 1**"), or following only negative UGIE ("**Group 2**"), based on the senior clinician-in-charge's individual investigative pathways.

6.2.2 CE procedure

CE was carried out with one of two commercially-available CE systems, PillCam®SB1/2 (Given®Imaging Ltd, now Medtronic, Minneapolis, Minnesota, USA) or Mirocam® (Intromedic, Seoul, South Korea). SB preparation was dependent on timing of CE relative to UGIE or colonoscopy, as well as the overall patient condition. In general, our centre's protocol has been to use 2L PEG, although an overnight fast alone was sometimes used for frailer patients. If CE was carried out immediately after colonoscopy, additional bowel preparation beyond the 2L PEG used for colonoscopy was not given. Simethicone was administered with

all CEs; use of prokinetics was guided by evolving practice guidelines and individual patient need[198]. Over this time period, CEs were read and reported by one of three experienced readers based at our centre using the relevant proprietary software. Speed and reading conditions varied as per individual preference. Significant CE findings were those deemed causative of the patient's presentation; this was determined by the senior treating clinician as they were best placed to weigh up the clinical presentation against the pathology seen. Significance of lesions seen was routinely recorded in the capsule report and/or patient casenotes at our centre. Significant findings included: vascular lesions (e.g. angioectasias), areas of fresh and ongoing bleeding seen at the time of CE, inflammatory lesions (e.g. ulcers, aphthae and strictures), various enteropathies such as NSAID-related enteropathy or portal hypertensive enteropathy, and discrete bleeding mass lesions. Over the study period, all CEs carried out at our centre have been recorded in a prospectively-designed database with the above details noted to be correct at time of CE.

6.2.3 Statistical analysis

Continuous data is reported as mean±standard deviation (SD) or median (range) where appropriate. Statistical analyses were carried out and normality of distributions was tested by plotting histograms using the Analysis Toolpak in Microsoft® Excel 2010 (Microsoft Corporation, Washington, USA). For normally distributed data, Student's T-test (when $n<30$) or the Z-test (when $n\geq30$) were used to compare means, whereas the Mann-Whitney U-test was used for data where a normal distribution could not be assumed. The Chi-square test was used to compare proportions for discrete data variables. A p-value of <0.05 was taken to denote statistical significance. No specific institutional ethical approval was required for this study as the data used had been collected in the course of routine patient care; ethical approval has been granted to the unit as a whole for the safe, confidential collection and storage of relevant patient information relating to CE.

6.3 Results

6.3.1 Characteristics of included patients

Over the period from March 2005-March 2017, 170 inpatients underwent CE for suspected small bowel bleeding (104M/66F, mean age 65.8±17.1 years). Forty-four patients had IDA and 126 had melaena. Mean haemoglobin level (Hb) at presentation was 82.8±22.4g/l. In total, there were 6 incomplete CEs; 2 were retained and required endoscopic or surgical retrieval. The median follow-up time was 31.1 months (range 0.03-121.4 months); however it must be noted that this was a continuously-maintained database and follow-up times depended on the time from CE to data collection for each patient.

Patients were divided into 2 groups for analysis of outcomes (**Figure 6.1**). *Group 1* comprised those with negative bidirectional endoscopy, while *Group 2* included those with only negative UGIE. The groups had similar admission Hb, demographics, and medical history; they were also followed-up for similar periods of time overall (**Table 6.1**).

Figure 6.1: Summary of patient selection and outcomes

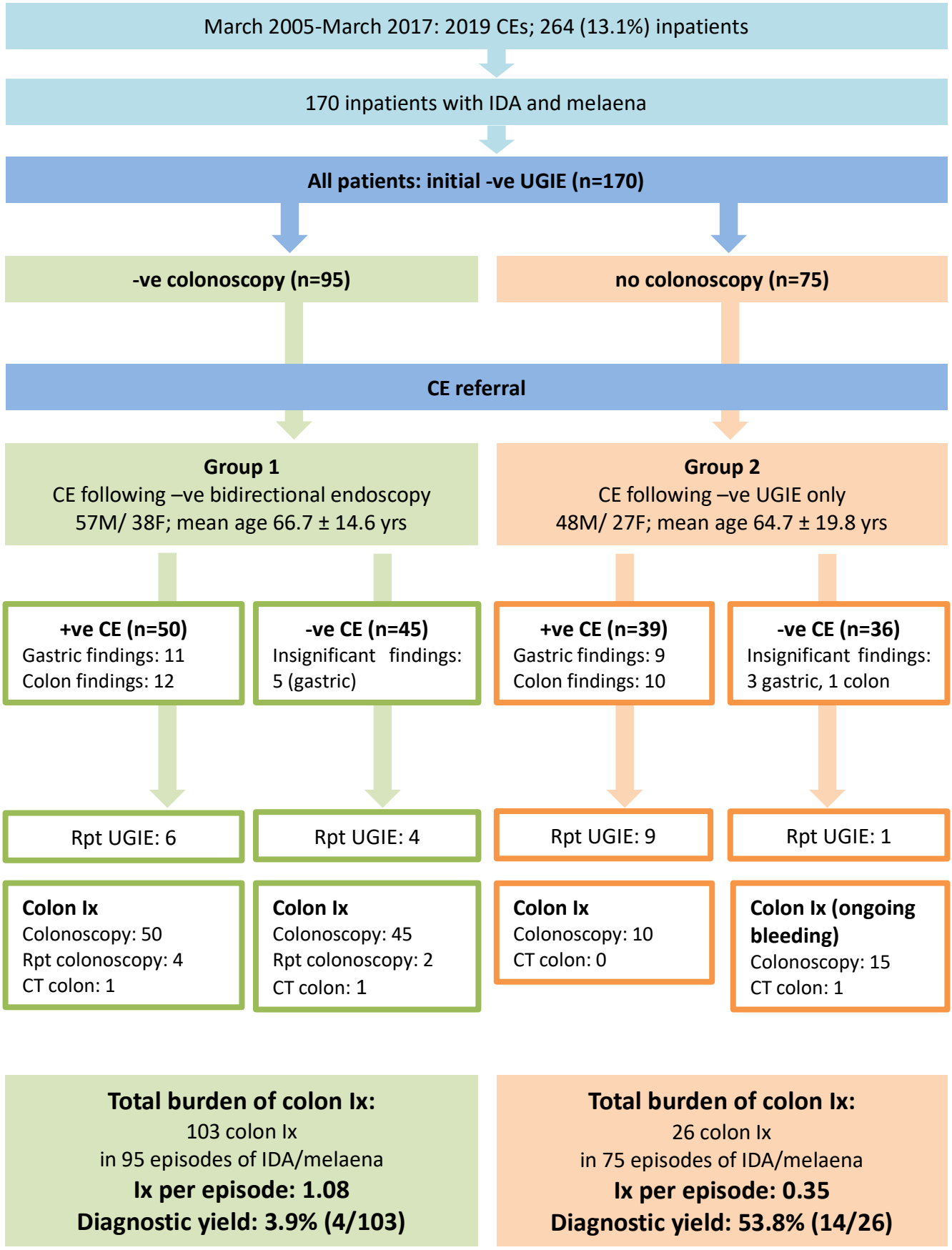


Table 6.1: Comparison of patient characteristics between patients undergoing CE following negative bidirectional endoscopy and patients undergoing CE following negative UGIE only

	Group 1: CE after negative bidirectional endoscopy	Group 2: CE after negative UGIE only	P-value
Total number	95	75	
M/F	57M/ 38F	48M/ 27F	0.59
Age; years (mean±SD)	66.7 ± 14.6	64.7 ± 19.8	0.46
PMH			
Liver disease	15	11	0.84
Cardiovascular disease	46	29	0.20
On anticoagulants/ antiplatelets	37 24 on anticoagulants 17 on antiplatelets	23 10 on anticoagulants 13 on antiplatelets	0.26
Renal disease	10	9	0.76
Previous episode/s of GI bleeding	28	24	0.72
Admission details			
OGIB (%)	48	50	**0.03**
IDA (%)	28	16	0.23
Other (%)	19	9	0.16
Symptomatic from blood loss (%)	31 (4 with haemodynamic compromise on admission)	38 (14 with haemodynamic compromise on admission)	**0.02** Haemodynamic compromise: **0.002**
Admission Hb; g/L (mean±SD)	82.8 ± 20.7	82.9 ± 24.6	0.98
Length of time from admission to CE; days (mean±SD)*	6.38 ± 3.80 (n=68)	5.08 ± 3.80 (n=66)	**0.02**
Total length of admission; days (mean±SD)*	12.5 ± 11.4 (n=68)	10.5 ± 9.58 (n=66)	**0.04**
Follow-up time after CE**; months (mean±SD)	37.9 ± 31.5	35.8 ± 31.9	0.62
CE findings			
Positive CE (%)	50	39	0.93
Negative CE (%)	45	36	
Incomplete CEs	3	3	0.77

Abbreviations: CE capsule endoscopy; Hb haemoglobin; IDA iron deficiency anaemia; OGIB obscure gastrointestinal bleeding; PMH past medical history; SD standard deviation

*These calculations include only from patients admitted specifically for OGIB/IDA; i.e. excluding patients admitted electively or with unrelated initial presentations.

**Follow-up as recorded in electronic hospital records – i.e. until time of last recorded patient contact, discharge (back) to another health board, or death.

Patients in *Group 2* were significantly more likely to have been admitted with melaena and were also significantly more symptomatic from blood loss at the time of admission. Outcomes and further investigations carried out within the two groups are summarised in **Table 6.2**.

Table 6.2: Investigations and management in the included group of inpatients with IDA/melaena

	Group 1: CE following -ve bidirectional endoscopy		**Group 2:** CE following -ve UGIE **only**	
CE findings	**+ve CE**	**- ve CE**	**+ve CE**	**-ve CE**
Number of pts (%)	**50 (52.6)**	**45 (47.4)**	**39 (52.0)**	**36 (48.0)**
Incomplete CEs (%)	3 (3.2)		3 (4.0)	
UGIE and Colonoscopy				
Missed findings on initial UGIE (%)	11 (22.0)	5 (11.1) *all insignificant	9 (23.1)	3 (8.3) *all insignificant
Missed findings on initial colonoscopy (**Group 1**) (%)	12 (24.0)	-	NA	
Colon findings on CE (**Group 2**) (%)	NA		10 (25.6)	1 (2.8) *insignificant
Repeat UGIEs (%)	6 (12.0)	4 (8.9)	9 (23.1)	1 (2.8)
Total number of colon procedures/ Ix carried out	Initial colonoscopy: 50 Repeat colonoscopy: 4 CT colon: 1 **Total: 55**	Initial colonoscopy: 45 Repeat colonoscopy: 2 CT colon: 1 **Total: 48**	Initial colonoscopy: NA Colonoscopy: 10 CT colon: 0 **Total: 10**	Initial colonoscopy: NA Colonoscopy: 15 CT colon: 1 **Total: 16**
Total burden of colon Ix	**103 colon Ix for 95 episodes**		**26 colon Ix for 75 episodes**	
Diagnostic yield of colon Ix	**3.9% (4/103)**		**53.8% (14/26)**	
Other Ix and/or management following CE				
DBE (%)	7 (14.0)	-	9 (23.1)	-
CT angiography (%)	5 (10.0)	3 (6.7)	1 (2.6)	2 (5.6)
Repeat CE (%)	-	-	2 (5.1)	-
Surgery (%)	5 (10.0)	2 (4.4)	4 (10.3)	-

Abbreviations: -ve negative; +ve positive; CE capsule endoscopy; DBE double balloon enterography; Ix investigations; SD standard deviation; UGIE upper gastrointestinal endoscopy

6.3.2 CE findings and outcomes: Group 1

In *Group 1*, there were 95 CEs carried out following negative bidirectional endoscopy. There were significant CE findings in 50 patients, i.e. diagnostic yield 52.6%. Of these patients, 46 had SB findings; 17/46 patients had additional non-SB findings detected by CE in the stomach (n=9; duodenitis, gastritis and GAVE), colon (n=6; all angiodysplasias and/or bleeding) or both (n=2). Another 4 patients had normal SB but colon findings seen on CE which were deemed relevant. Forty-five patients had nondiagnostic CE following negative bidirectional endoscopy. In 31, the SB was reported as normal whereas the other 14 had nonspecific findings thought unlikely to be of clinical significance. The indication for CE was melaena in 67 patients and IDA in 28. The proportions of patients with melaena and IDA with or without significant CE findings were not significantly different (see **Table 6.2**). **Table 6.3** gives the breakdown of CE findings in this group.

Table 6.3: Breakdown of CE findings in Group 1

Significant CE Findings (n=50)	
Type of findings	**Number of patients (%)**
AVM/angiodysplasia	18 (36%)
Free blood/active bleeding	10 (20%)
Duodenal ulcer	1 (2%)
Enteropathy, ?NSAID/other medication-related	1 (2%)
PHE including SB varices	9 (18%)
SB inflammation	2 (4%)
Significant-appearing SB lesion e.g. polypoid masses	5 (10%)
Normal SB but findings elsewhere in gut	4 (all colonic bleeds/AVMs) (8%)
Nondiagnostic CE Findings (n=45)	
Type of findings	**Number of patients (%)**
Normal capsule endoscopy	31 (69%)
AVM not deemed clinically significant	6 (13.3%)
Nonspecific changes/findings e.g. mild inflammation, small phlebectasias, minor mucosal congestion	5 (11.1%)
Benign-appearing/previously-known SB polyp	2 (4.4%)
Non-critical fibrotic stricture	1 (2.2%)

Therefore, in this group CE found a total of 16/95 (16.8%) gastric findings which had been missed on initial UGIE. Ten patients had repeat UGIE; in 9/10 the UGIE was done to further investigate or manage lesions seen on CE while 1 was a "second look". There were missed colon findings in 12/95 (12.6%) patients, of whom 3 required repeat colonoscopy for APC; the others were managed conservatively for confirmed or likely diverticular bleeds. A further 3 patients had repeat colonoscopies due to re-bleeding and/or ongoing bleeding, i.e. 6/95 patients had repeat colonoscopies. Two patients underwent CT colonography following CE. Double balloon enteroscopy (DBE) was performed on 7 patients in this group to manage SB lesions seen on CE. Seven patients required surgery to investigate discrete lesions seen on CE (n=3) or to manage continued bleeding (n=4).

6.3.3 CE findings and outcomes: Group 2

In *Group 2*, seventy-five CEs were performed in patients who had negative UGIE only, with a diagnostic yield of 39/75 (52.0%). In the 39 patients with significant CE findings, 6/39 had normal SB but significant non-SB findings in the stomach (n=2) and colon (n=4). Of the 33 patients with SB findings on CE, 9/33 had additional non-SB findings in the stomach (n=3), colon (n=2) or both (n=4). Of the 36 patients with nondiagnostic CE, the SB was reported as normal in 28. Three patients in this subgroup had additional non-SB findings (which were considered insignificant): 2 in the stomach and 1 patient with findings in both stomach and colon. The indication for CE was melaena in 59 patients and IDA in 16. Patients with nondiagnostic CE findings were significantly more likely to have undergone CE for melaena rather than IDA, compared to patients with significant CE findings (p=0.03). **Table 6.4** provides the breakdown of CE findings in this group.

Table 6.4: Breakdown of CE findings in Group 2

Significant CE Findings (n=39)	
Type of findings	**Number of patients (%)**
AVM/angiodysplasia	13 (33.3%)
Free blood/active bleeding	11 (28.2%)
Enteropathy, ?NSAID/other medication related	1 (2.6%)
PHE including SB varices	5 (12.8%)
Significant-appearing SB lesion e.g. polypoid masses	3 (7.7%)
Normal SB but findings elsewhere in gut	6 (2 gastric findings; 4 caecal/colon bleeding) (15.4%)
Nondiagnostic CE Findings (n=36)	
Type of findings	**Number of patients (%)**
Normal capsule endoscopy	28 (77.8%)
AVM not deemed clinically significant	6 (16.7%)
Nonspecific changes/findings e.g. mild inflammation, small phlebectasias, minor mucosal congestion	2 (5.6%)

There were 12/75 (16.0%) gastric findings missed by initial UGIE. Ten patients underwent repeat UGIE. Six UGIEs were done to target lesions seen on CE (3 of these were push enteroscopies to reach the duodenum). 11/75 (14.7%) patients had new colon findings; all these findings were arteriovenous malformations (AVMs) and/or colonic bleeding. Overall in this group, 25 patients underwent colonoscopy following CE. Seven colonoscopies were done to target lesions seen on CE while the remainder were carried out in patients experiencing continued bleeding or symptoms. 14/25 colonoscopies found likely causes for the patients' presentations; notably, one patient was found to have a colon adenocarcinoma. In the patients with negative colonoscopies, most were managed conservatively with spontaneous resolution of bleeding in 6; in 2 patients repeat UGIE found the likely sources of blood loss. One patient had CT colonography following normal CE with no cause found.

Nine patients underwent DBE to further investigate discrete lesions seen on CE (n=3), manage SB angioectasias (n=3) and further investigate/manage an area of active SB bleeding seen on CE (n=3). Four patients had surgery for lesions seen on CE.

6.3.4 Comparison of colon investigations per episode of GI bleeding between the two groups

In *Group 1*, a total of 103 colon investigations (colonoscopies and CT colonographies) were performed for 95 inpatient episodes of suspected small bowel bleeding, giving a rate of 1.08 colon investigations per episode. The overall diagnostic yield of these colon investigations was 3.9%. Using the alternative approach in *Group 2*, 26 colon investigations were performed for 75 inpatient episodes of suspected small bowel bleeding, i.e. 0.35 colon investigations were carried out per episode. The diagnostic yield in this group was 53.8%.

6.3.5 Length of time between admission and CE

Examining only data from patients admitted for GI bleeding (excluding elective admissions and patients with unrelated initial presentations who developed GI bleeding during their hospital stay), patients in *Group 2*, undergoing CE following negative UGIE only, had significantly shorter mean times from admission to CE compared to patients in *Group 1* (5.08±3.80 vs 6.38±3.80 days; p=0.02) and shorter overall admission length (10.5±9.58 vs 12.5±11.4 days; p=0.04). This was despite patients in *Group 2* being more symptomatic of blood loss at the time of admission, including a greater proportion of patients displaying haemodynamic compromise when admitted (14/75 patients in *Group 2* vs 4/95 patients in *Group 1*; p=0.002).

6.4 Discussion

6.4.1 Impact on admissions

In this study, the earlier use of CE for inpatients with melaena or IDA, following negative UGIE, reduces the need for subsequent colonoscopy and shortens admission times. Previous data from Singh et al[36] in a group of 144 inpatients has shown that the earlier use of CE (within 3 days of admission) was associated with higher diagnostic yield, rates of therapeutic intervention and decreased length of stay. Similarly, the patients who underwent CE earlier in the diagnostic pathway also had a significantly shorter mean length of stay by about 2 days ($p=0.04$). This translates to potentially significant cost savings or at least increased patient turnover and therefore capacity, especially important in large hospitals with high patient caseload. In a 2006 study by Marmo et al[203], soon after the introduction of commercial CE, patients undergoing CE for obscure GI bleeding (OGIB) required a mean of 1.7 hospital admissions to reach a positive diagnosis, with a mean of 15.5 days of hospital stay; 42% had more than one colonoscopy; 44.6% had 2 or more UGIEs. Hospital admissions were the biggest cause of resource utilisation in their group of patients, followed closely by colonoscopies and UGIEs. It is however acknowledged that cost-savings would vary between countries and healthcare systems as the cost of CE may not be adequately reimbursed at some centres.

6.4.2 Impact on investigative burden

The reasons for the shortened length of stay in patients in Group 2 could be related to the additional time required to perform both upper and lower GI endoscopies before making the decision to proceed to CE. Therefore, the early use of inpatient CE was useful in guiding the choice of the next most appropriate route of investigation or management, as well as aiding the decision whether to proceed with these investigations and interventions urgently or following discharge. Similarly, in previous studies where CE was used acutely or semi-acutely to investigate GI bleeding (**Table 6.5**), CE findings showed good correlation with subsequent UGIE where CE was performed as a first-line investigation before any other endoscopies[12,13,204–206]; CE carried out after endoscopic imaging was effective in directing the subsequent route of investigation[11,126,207–211].

These findings are corroborated by this study. Patients in Group 1 underwent 3.13 as many colon investigations per admission for IDA or OGIB compared to those in Group 2; however in Group 2, the use of CE earlier in the diagnostic pathway increased the DY of the resulting colonoscopies. Moreover, no adverse outcomes related to colon pathology were reported in those patients who did not have colon investigations following CE. Notably, our study reports a higher completion rate with 6 incomplete CEs and only 2 retained capsules in 170 inpatient CEs, compared to previously-quoted inpatient completion rates of 50% by Dunnigan et al[40] and 68.6% from Yazici et al[39]. This therefore implies that in selected patients with IDA or melaena, without frank rectal bleeding or other such signs or symptoms suggesting lower GI tract pathology, CE could be used as a diagnostic or screening tool following initial UGIE, allowing completion colonoscopy to be carried out on a less urgent, outpatient, basis. The results of CE were able to assist clinicians in determining the next most appropriate investigation, with no missed diagnoses in our group of patients. Overall this would help to optimise resource use and relieve some pressure on already overburdened systems, especially in the NHS.

The advantages of such an approach are appealing as a significant proportion of patients with GI bleeding or suspected GI bleeding have been shown to require multiple investigations. Woodward et al conducted an analysis on the length of endoscopic workup in a large group of 451 470 patients presenting with GI bleeding[212]. A quarter of these patients required more than one procedure to investigate and/or manage GI bleeding, with an average of 2.4 procedures per patient. In particular, patients with anaemia were the least likely to be managed with a single procedure, with 20 and 21% of these patients requiring further UGIEs and colonoscopies respectively. Similarly, in a 2015 study, Sonnenberg modelled test sequences in patients with GI bleeding, and found an average of 2.7 procedures performed per patient, with a significant 5% of patients requiring more than 6 procedures[213].

An alternative approach to CE is for patients with ongoing GI bleeding to undergo repeat UGIE and colonoscopy; this would be supported by the incidence of “missed” upper and lower GI findings seen in our group. This approach is in line with work by Fry et al[214], but on the other hand is not suggested by the current guidelines, and would be limited by increased investigative burden and poor patient acceptability. Furthermore, the current convention of performing colonoscopy before CE is based on older, possibly now less-supported data that suggest the small bowel is the bleeding source in 10% of GI bleeding[20]. With the technological advances now available, it could be suggested that the increasing accessibility of CE as a

diagnostic test is combined with comprehensive clinical assessment to ensure an appropriate and timely choice of investigation for patients with GI bleeding.

6.4.3 Limitations

Limitations of this study stem largely from its retrospective design including missing data, dependence on good prior record-keeping and the possible effects of advances in CE technology since its introduction to clinical practice. However, although image quality may have improved over the study period, the main finding of concern in patients with GI bleeding is the localisation of blood within the GI tract rather than detailed lesion definition; this is an obvious finding where technological improvement may not have had as great an impact. Furthermore, our centre's data date from 2005, when CE had already been approved for conventional clinical use, with acceptable image quality from the first models which we had used. Similarly, our centre had started using PEG for bowel preparation at an early stage, almost from the beginning of the capsule service, even though official guidelines had not been standardised then; most of the patients in our group received similar bowel preparation throughout the study period.

Another limitation stemming from the retrospective study design is that the choice of investigative pathway and CE timing in our patients was determined by consultant preference. Despite this, the demographics and admission data suggest that the two groups were comparable. Given that melaena was more often the indication for CE in Group 2, our results would also suggest that such patients with melaena and negative UGIE are more likely to benefit from earlier use of CE. Although this approach seems logical, in routine clinical practice, most centres currently reserve the use of CE until a negative colonoscopy has occurred. Furthermore and despite the recognised disadvantages of a retrospective study, such a study has the benefit of a large patient group, longer follow-up times and accurate reflection of the "real world" experience.

Table 6.5: Summary of previous studies on use of CE in the acute to semi-acute setting

Authors, Year[ref]	Type of study	No. of patients (completion rate)	CE model	Indications for CE	Ix before CE	Time to Ix	Positive CEs	Management of positive CEs	Negative CEs	Management of negative CEs	Follow-up period and outcomes
Studies where CE was used following negative conventional endoscopy											
Lecleire *et al*, 2012[207]	Retrospective, single centre	55 (100%)	PillCam® M2A and SB	Malaena, haematochezia, haemodynamic instability, >2 units RCC transfused	Negative bidirectional endoscopy	CE within 48h of negative bidirectional endoscopy	49	Endoscopy: 30 (26 PE/DBE) Surgery: 12 Conservative: 7	6	Interventional radiology: 1 Conservative: 5	36 months 6 patients rebled
Rauf *et al*, 2014[208] (abstract)	Single centre	25 (100%)	NS	Acute OGIB	Negative bidirectional endoscopy	NS	24	APC: 5 Surgery: 4 Conservative: 16	1	NS	NS
Ponte *et al*, 2015[209] (abstract)	Single centre	42 (100%)	NS	Active overt OGIB, persistent maelaena/ haematochezia, haemodynamic instability, >2 units RCC transfused	Negative bidirectional endoscopy	CE within 48h of negative bidirectional endoscopy	38	Targeted treatment/ management in 31 patients	4	NS	NS
Perez-Cuadrado Robles *et al*, 2015[126]	Retrospective, single centre	16 (100%)	PillCam®SB	Haematemesis, haematochezia, malaena	Negative bidirectional endoscopy; other negative investigations: 8 DBE, 3 PE, 12 CE, 21 radiological imaging	All patients proceeded to DBE following CE, within 48h of presentation	16	All underwent DBE: CE changed approach in 3 patients (DY 16/16)	0	-	NS 5 rebled 4 tumours found: all treated surgically
Schlag *et al*, 2015[11]	Prospective, single centre	20 (95%)	PillCam®SB2	Malaena or dark red stools, haemodynamic instability, Hb drop >2g/dL,	UGIE only	9.8h to UGIE (mean)	15	Enteroscopy: 10 Surgery: 1 Colonoscopy: 4 (DY 3/4)	4	Colonoscopy (DY 3/4)	4 weeks 1 death (cardiac), 1 readmission (diverticular bleed)

				transfusion >2 units RCC/day (Excluded: haematemesis, fresh rectal bleeding)							
Studies where CE was used as first-line investigation for bleeding											
Gralnek *et al*, 2013[204]	Prospective, multicentre	47 (97.9%)	PillCam®ESO2	Haematemesis and/or malaena in past 48h (Excluded: unstable patients, fresh haematemesis)	None	CE within 12-24h	31	UGIE (DY 27/31)	15	UGIE (DY 12/15)	NS
Gutkin *et al*, 2013[205]	Prospective, single centre	12 (100%)	PillCam®ESO2	Malaena, haematemesis, haemodynamic instability (Excluded: Haematemesis <2h before presentation, too unstable)	None	NS	8	UGIE (DY 8/8)	4	UGIE No high risk stigmata seen	NS
Meltzer *et al*, 2013[13]	Prospective, single centre	24 (100%)	PillCam®ESO2	Malaena, haematemesis (Excluded: Haemodynamic instability)	None	NS	11	UGIE (DY 7/11)	8	UGIE (DY 1/8)	24h No complications
Chandran *et al*, 2013[206]	Prospective, multicentre	83 (100%)	PillCam®ESO	Malaena, haematemesis (Excluded: too unstable)	None	15h to CE (median)	41	UGIE (DY 41/41)	42	UGIE (DY 21/42)	NS 4 patients rebled
Sung *et al*, 2016[12]	Prospective, single centre	34 (100%)	PillCam®ESO2	Coffee ground vomit, malaena (Excluded: fresh haematemesis, haemodynamic instability)	None	NS	7	UGIE (DY 7/7)	27	UGIE No significant findings	30 days No rebleeding. 1 patient with negative CE later had gastric ulcer
Order of CE in diagnostic pathway not defined											
Dunn *et al*, 2014[210] (abstract)	Retrospective, single centre	127 (100%)	NS	All urgent CE referrals	NS	NS	57	NS	70	NS	NS
Omote *et al*, 2014[211] (abstract)	Retrospective, single centre	35 (100%)	NS	Acute overt OGIB	NS	NS	21	Enteroscopy: 10	14	NS	NS No severe complications

Abbreviations: CE capsule endoscopy; DBE double balloon enteroscopy; DY diagnostic yield; PE push enteroscopy; RCC red cell concentrate; UGIE upper gastrointestinal endoscopy

6.5 Conclusion

In conclusion, inpatient CE for IDA or melaena had a diagnostic yield of 52.3% at our centre. In such patients, the use of CE earlier in the investigative pathway significantly reduced the number of urgent inpatient colonic investigations performed, without compromising clinical outcomes in our study cohort. This has the potential to improve the patient experience by reducing the number of negative invasive procedures, and by allowing further investigations such as completion colonoscopy to be carried out at a later date or admission. Following on from this, this study found that the earlier use of CE also shortened hospital stays. The findings inspire confidence in the earlier use of CE in inpatients with IDA or melaena in the absence of signs and symptoms suggestive of colonic pathology.

Chapter 7 Role of CE in young patients with IDA

The previous chapter has shown that the timing of CE examination in the diagnostic pathway for SBB can be better utilised to improve diagnostic yield and patient outcomes. In this next chapter, I aim to examine how judicious patient selection can also improve the clinical utility of this mode of investigation.

7.1 Introduction

Previous CE studies have shown that the aetiology of GI blood loss differs with patient demographics. Young patients – defined in this work as those aged 50 years and below – are more likely to bleed from SB malignancies, Dieulafoy lesions, Meckel's diverticuli diverticula, polyps or Crohn's Disease (CD). Conversely, those older than 40 are more likely to have angioectasias or non-steroidal anti-inflammatory drug (NSAIDs)-induced ulceration[27–29].

Therefore, although young patients represent a small proportion of patients undergoing CE, previous data from our tertiary care centre has shown that they are more likely in the event of a diagnosis to have significant diagnoses including SB tumours[28]. Moreover, only a couple of studies focusing on young IDA patients undergoing SB evaluation are available to date[28,29]. This retrospective study aimed to estimate the DY of CE for SB pathology – in particular, the prevalence of SB neoplasia – in a large cohort of young patients (age ≤ 50 years) with IDA and negative bidirectional GI endoscopy. It also aimed to assess possible predictive factors associated with the occurrence of significant SB pathologies.

7.2 Methods

7.2.1 Patient selection

This was a retrospective study. High-volume SBCE providers (> 100 CE cases/ year) were invited to contribute data on consecutive patients undergoing SBCE between 2010-2015. These centres were invited from the ESGE SB Working Group's research network.

Inclusion criteria were: age 19-50 (inclusive), presenting with IDA based on the World Health Organization criteria (Hb < 13 g/dL in men and < 12 g/dL in women, with evidence of iron deficiency: MCV < 80 or ferritin < 12-15 µg/l), and negative upper and lower GI endoscopy evaluation.

Exclusion criteria were: history of previous (or ongoing) obscure-overt GI bleeding (to homogenize the included patients), patients referred for SBCE for indications other than IDA, or presence of any comorbidity that could also cause IDA (e.g. known inflammatory bowel disease, coeliac disease, end-stage renal failure, prosthetic heart valve). Only women with recent complete gynecological evaluation (to exclude any cause of excessive gynecological blood loss) were included.

7.2.2 Data collection

Structured data collection questionnaires were sent to all participating centres. The data collection form which was sent out is shown in **Appendix I** and the participating centres are detailed in **Appendix II**. Data were collected on patient demographics (age, gender), medical history including weight loss and comorbidities, indications for CE, investigations performed before CE [Hemoglobin(Hb) at time of SBCE and lowest recorded value if available, mean corpuscular volume (MCV), GI endoscopies/cross-sectional imaging, duodenal biopsies/coeliac serology], medications (NSAIDs, antiplatelet agents, warfarin/heparin), findings, final diagnosis and outcomes (if known or if followed-up within the study period). CE videos were analysed by local readers as part of standard clinical care; no further central CE reading was performed.

Local investigators were asked to categorise findings according to their clinical relevance using the Saurin score[93]. CE examinations were deemed positive when containing at least one P2 SB finding, i.e. a finding which could explain symptoms and/or guide further workup. For the purpose of further analysis, P2 CE findings were eventually categorized as: neoplastic or

non-neoplastic but clinically significant. In order to allow for variations in practice between participating centres and to accommodate missing data, a minimum data set was defined for inclusion: patients had to have had Hb at time of SBCE, MCV, negative bidirectional GI endoscopies and CE results.

All patient identifiable data were anonymized during collection. No specific ethical approval needed to be obtained as all data were collected during routine patient care.

7.2.3 Statistical analysis

Continuous variables are presented as means (SD) or medians (IQR), as appropriate. Categorical variables are presented as numbers (%). Due to the number of variables, CE findings were analyzed by multivariate logistic regression using 5 multiple imputed datasets to adjust for missing values of ferritin and lowest recorded Hb in some patients. This allowed maximal use of data while minimizing bias from missing values[215,216]. Further variable selection was done using backwards elimination. For model comparison, the log likelihood test was used with a P-value of 0.157 deemed to be of statistical significance[217,218].

7.3 Results

7.3.1 Included patients

Cases were collected from 18 centres in 12 countries. Data on 389 patients (262F/127M; mean age 39.4±9.3 years) were scrutinized. 220 patients (122F/98M; mean age 40.5±8.6 years) had sufficient data for inclusion in the final analysis, as defined by the minimum data set (**Figure 8.1**). The patients' clinical characteristics are summarized in **Table 8.1**. At presentation, the mean Hb for the patient group was 9.27±2.36 g/dL, mean MCV was 71.54±9.59 fL and mean ferritin was 13.16±29.65 µg/L.

Figure 7.1: Patient selection and inclusion for this study

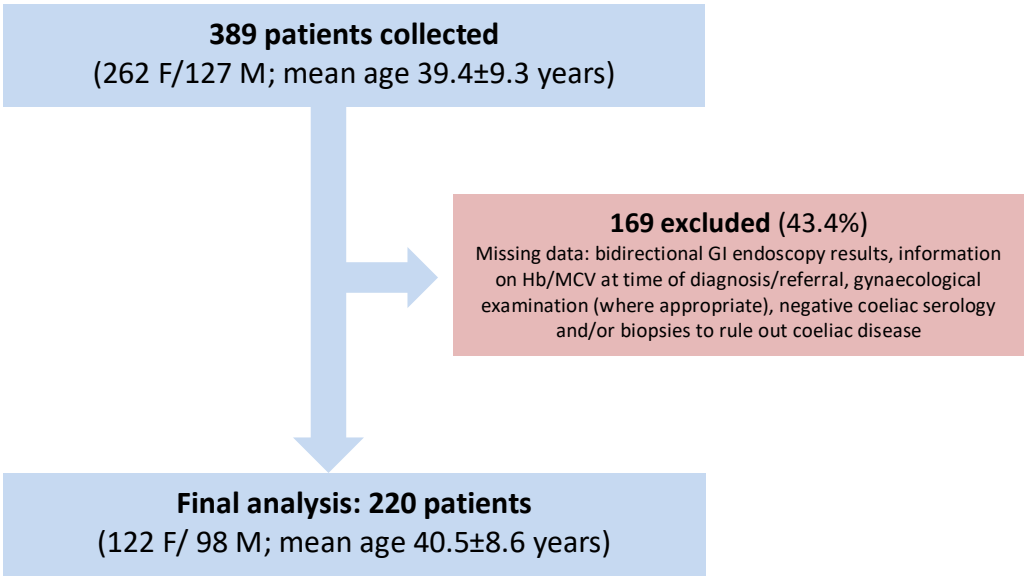


Table 7.1: Characteristics of included patients (n = 220)

The number of patients is specified where data was not available for all patients.

Demographic details	
Gender	122 F/98 M
Age (mean ±SD), years	40.5±8.6
Past medical history	
Gastrointestinal disease n(%)	38 (17.3%)
Cardiovascular disease n(%)	25 (11.4%)
Previous malignancy n(%)	5 (2.3%)
Renal disease n(%)	2 (0.9%)
Other past medical history n(%) e.*g. diabetes, rheumatological conditions*	65 (29.5%)
Family history of GI malignancy n(%)	23 (10.5%)
Characteristics at presentation	
Patients presenting with weight loss n(%)	17 (7.7%)
Hb at presentation (mean±SD)	9.27±2.36 g/dL
Lowest Hb recorded (n = 193) (mean±SD)	8.53±2.2 g/dL
MCV at presentation (mean±SD)	71.54±9.59 fL
Ferritin at presentation (n = 181) (mean±SD)	13.16±29.65 µg/L
Relevant medications n(%)	None: 201 (91.4%) Yes: 19 (8.6%) Antiplatelet medications (aspirin/clopidogrel): 7 NSAIDs: 7 Anticoagulants: 5 More than 1 medication: 2
Prior imaging investigations	
Patients previously investigated with CT abdomen n(median; range)	60 (1; 1-3)
Patients previously investigated with MRE *n*(median; range)	15 (1; 1-3)

Abbreviations: CT computed tomography, Hb haemoglobin, MCV mean corpuscular volume, MRE magnetic resonance enterography, NSAIDs non-steroidal anti-inflammatory drugs, SD standard deviation

7.3.2 Diagnostic yield of CE in young patients with IDA

Among the 220 patients, 71 had a positive CE (DY 71/220; 32.3%). Subsequently, patients with positive CE were divided according to final diagnosis into 2 groups (**Figure 7.2**): patients with neoplastic SB pathology (10/220; 4.5%), and non-neoplastic albeit clinically significant CE findings (61/220; 27.7%). The most common non-neoplastic but significant findings were SB angioectasias (22/61) and SB Crohn's disease (15/61) (**Table 7.2**). In total, 17 patients reported weight loss at presentation. Two of this group eventually had neoplastic pathology and 9 had non-neoplastic but significant findings, i.e. 2/10 (20%) of patients with neoplasia presented with weight loss, compared to 9/61 (14.8%) of patients with non-neoplastic findings and 6/149 (4%) of patients with normal or insignificant findings. In the patients with neoplasia, 6/10 had undergone CT or MR imaging prior to CE with no pathology yield (hence the investigation with CE). 22/61 of patients with significant non-neoplastic pathology, and 40/149 of patients with normal CE, had had previous CT or MR imaging.

Figure 7.2: Summary of CE findings in study group

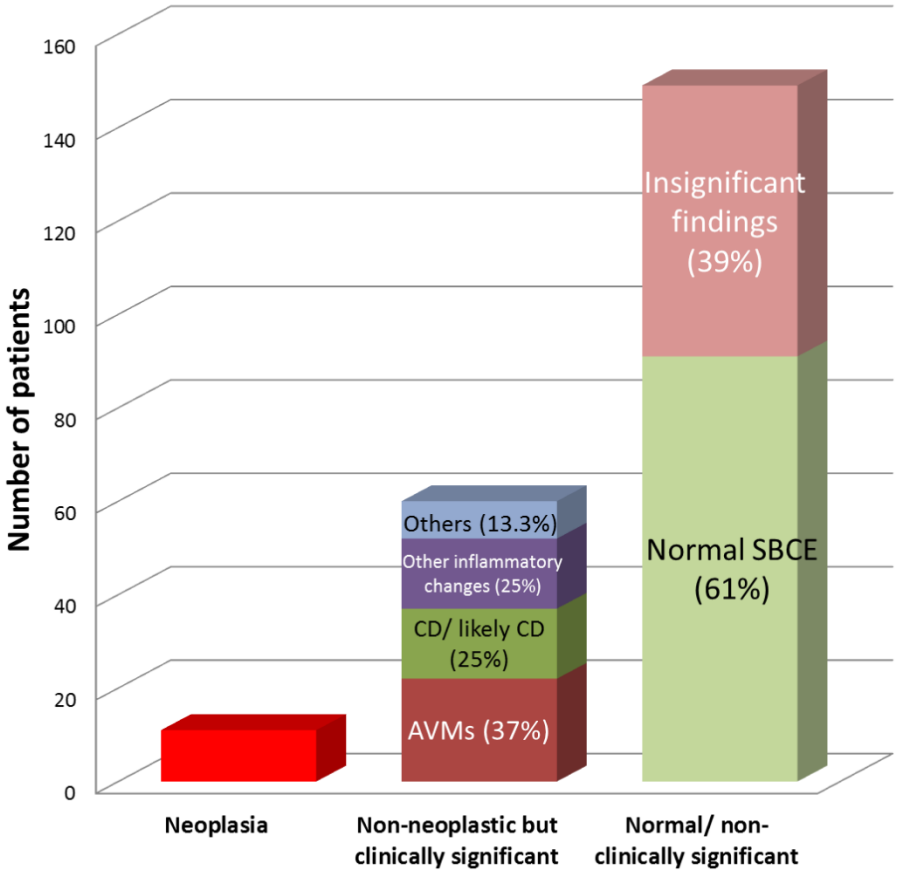


Table 7.2: CE small bowel findings in study group

Type of findings	Number of patients (%) Details below
Neoplastic	10 (4.5%) Malignant neoplasia: 4 adenocarcinoma, 3 GIST, 1 lymphoma Benign neoplasia: 1 Vanek tumour, 1 hamartoma
Non-neoplastic (clinically significant)	61 (27.7%) 22 angioectasias, 15 Crohn's Disease, 5 nonspecific inflammation, 5 ulcers, 5 NSAID enteropathy, 9 others (2 Meckel's, 1 inflammation due to rheumatoid arthritis, 1 coeliac, 1 strictures, 1 Dieulafoy lesion, 1 hereditary haemorrhagic telangiectasia, 1 pinworms, 1 mucosal bulge)
Normal/ minimal and not clinically significant	149 (67.7%) 91 normal, 58 minor/insignificant findings (e.g. lymphangiectasias, red spots)

7.3.3 Predictors of significant SB pathology

All possible predictive factors included were subjected to variable selection to identify the best predictors of significant SB pathology (both neoplastic and non-neoplastic). These were: ferritin, MCV, presence of weight loss and use of antiplatelet pharmacologic agents (supplementary material). On multivariate analysis (**Table 7.3**), lower MCV was associated with clinically significant SB pathology (OR 0.96; 95%CI 0.92-0.99; P=0.03), i.e. the odds of diagnosing significant SB pathology in CE were increased 4% for every unit of decrease in MCV. Furthermore, the presence of weight loss at clinical presentation increased the odds of significant SB pathology 3.85 times (OR 3.85; 95%CI 1.31-11.13; P=0.01). Lastly, this model suggests a possible association between the use of antiplatelet medications and the presence of significant findings (OR 3.74; 95%CI 0.765-18.313; P=0.10); however, due to the small number of patients receiving this specific pharmacological treatment, no valid conclusion can be drawn.

Table 7.3: Predictive factors for significant SB findings in young patients with IDA

Variables in initial model	OR	SE(logOR)	Pr(>|t|)	95% CI
(Intercept)	2.226	1.26	0.530	0.188-26.301
Weight Loss (Y/N)	3.857	0.55	0.010	1.313-11.336
Initial MCV	0.961	0.02	0.030	0.924-0.999
Antiplatelet use	3.743	0.81	0.100	0.765-18.313
NSAID use	2.586	0.94	0.310	0.410-16.320
Lowest Hb	1.150	0.09	0.120	0.964-1.372

Abbreviations: CI confidence interval, Df degrees of freedom, Hb haemoglobin, MCV mean corpuscular volume, NSAID non-steroidal anti-inflammatory drug, OR odds ratio, SE standard error

7.3.4 Patient outcomes

In this cohort, 136/220 patients had resolution of IDA on follow-up (which was variable between centres). At the time of writing, 18/220 were lost to follow-up. **Table 7.4** details outcomes for this patient group following CE. Seven of the 10 patients diagnosed with neoplasia had resolution of IDA following surgical management. Of the 3 in whom IDA did not resolve, 2 were diagnosed with adenocarcinoma and 1 had been diagnosed with a hamartoma.

Table 7.4: Patient outcomes following CE

Group (n=patients where information on follow-up was available)	Resolution of IDA		No Resolution	
	Active treatment	Conservative management only	Active treatment	Conservative management only
Neoplastic pathology (n=10)	7: all surgical management	-	2: further enteroscopy (1 for retrieval of retained capsule, 1 for biopsy) 1: surgical resection	-
Non-neoplastic but significant pathology (n=57)	14: treatment for CD 10: further enteroscopy 4: repeat ileocolonoscopy 2: repeat CE 1: repeat UGIE 5: surgical management	13	9: further SB evaluation with deep enteroscopy	5
No significant pathology (n=135)	2: repeat ileocolonoscopy 1: Meckel's scan	82	2: further SB evaluation 1: repeat CE 1: repeat UGIE and ileocolonoscopy	45

Abbreviations: CD Crohn's Disease; CE capsule endoscopy; SB small bowel; UGIE upper gastrointestinal endoscopy

In the group of patients with non-neoplastic but clinically significant pathology, 44/61 (72.1%) had IDA resolution on follow-up. Eighteen of these 44 patients required further GI endoscopy (UGIE, ileocolonoscopy, repeat CE and/or deep enteroscopy including push enteroscopy and double-balloon enteroscopy). Five patients required surgical management: 2 underwent resection of Meckel's diverticulae diverticula, 1 required surgery for removal of the retained capsule, 1 had haemorrhoids banded and 1 underwent SB resection for CD. Thirteen out of 44 patients were managed conservatively; 10 had angioectasias, 2 had nonspecific SB inflammation and 1 had pinworms. Thirteen out of 61 patients with non-neoplastic but clinically significant pathology (21.3%) did not have resolution of IDA on

follow-up. Seven of these 13 patients had angiodysplasias. In this group, 9/13 had undergone further SB evaluation by deep enteroscopy.

85/149 (57.0%) patients with no significant pathology on CE had resolution of IDA on follow-up. 82 of these patients were managed conservatively; 2 underwent further ileocolonoscopy and 1 had a negative Meckel's scan.

7.4 Discussion

7.4.1 Causes of SB blood loss in young patients with IDA

A significant proportion of patients with IDA (approximately 30%) remain undiagnosed following bidirectional GI endoscopy, prompting SB evaluation[23]. The results of this study are in agreement with existing studies on the epidemiology of SB blood loss and show that younger patients, presenting with IDA, are at higher risk of SB neoplasia compared to older patients. Zhang *et al* found that SB angioectasias, while the most common cause of OGIB in patients aged >65 and accounting for 54% of cases, were present in only 9% of patients 40 years old or less[35]. Likewise, only 10% (22/220) of patients in our cohort were found to have SB angioectasias. In contrast, about 5% of the patients in this study had SB neoplasia, similar to the estimated population prevalence of 3-9%[30,31]. Previously, it has been reported at our centre that sinister or significant pathology appears in 25% of patients below 40 years old but only 7.5% of patients over 40 years[28].

A study by Sidhu *et al* demonstrated angioectasias in 10% of patients younger than 50 years old who underwent CE for IDA, and SB tumors in 3% of the same patient cohort[29]. Interestingly, SB angioectasias are known to occur more frequently alongside other comorbidities including cardiovascular disease, chronic kidney disease and/or chronic respiratory conditions; consequently, SB angioectasias may be less common in younger, fitter patients such as our group[219]. Therefore, this large multicenter study underscores the importance of having a high index of suspicion in young patients presenting with IDA.

7.4.2 SB neoplasia

Small-bowel neoplasia was the diagnosis considered the most significant in this group of young patients. Of the 10 patients from this cohort diagnosed with neoplasia, 8 had malignant histopathology. According to US and UK data, carcinoid tumors and adenocarcinomas are the most common SB neoplasias[32,33]. The UK data also show an increasing incidence of SB tumors since the 1980s[33]. The prognosis of SB malignancy remains poor; for example SB adenocarcinoma still has a 5-year survival of less than 30%[32]. This could be due to factors such as location of the malignancy – significant proportions of these SB tumors were located in the ileum, thus out of reach of conventional endoscopy[33] – and the resulting diagnostic delay [220]. Modlin *et al* found patients with SB carcinoid tumors were more

likely to have disseminated disease at diagnosis compared to gastric carcinoids. The same study showed minimal change in survival rates for carcinoid tumors over the past 50 years, implying failure to identify these lesions in a timely manner, or a lack of information to guide effective treatment[221].

7.4.3 Predictive factors for significant SB findings

Notably, only a small proportion of patients in our group had weight loss as a symptom at the time of presentation and only 2 out of 10 patients with neoplastic pathology experienced weight loss. This emphasizes the minimal or nonspecific symptoms which SB malignancies initially present with[30]. On the other hand, a larger proportion (20%) of the group with neoplastic diagnoses reported weight loss compared to patients with significant non-neoplastic pathology (14.8%) and those with normal CE results (4%). These differences suggest that young patients presenting with weight loss should be investigated more extensively and earlier.

To the best of my knowledge, there are few studies attempting to quantitatively correlate risk of significant SB findings with red cell indices as markers of IDA. As MCV decreased, there appeared to be a proportionate increase in the likelihood of SB tumors. In anaemic patients the probability of IDA increases with decreasing MCV[222]. This could be related to the duration of IDA, or because the anemia had failed to resolve over a period of time thus indicating ongoing or progressive pathology. For such patients with more severe IDA, the current UK guidelines suggesting 1-3 months of empiric oral iron replacement therapy following negative bidirectional endoscopy may cause further diagnostic delay.

7.4.4 Limitations

Limitations of this study include its retrospective study design, meaning that clinical data were incomplete for several patients (almost half in the included cohort). This could have led to some overestimation of results. This potential effect has been minimized as far as possible using multivariate analysis as detailed. Secondly, many of the participating centers were high-volume or tertiary referral centers, which would therefore have taken a disproportionate number of complex patients or those suspected of having sinister pathology. Finally, this study used MCV as a marker of iron deficiency in anemic patients although drawbacks exist

to the use of MCV to quantify iron-deficiency. Other red cell indices such as mean cell hemoglobin (MCH) (i.e. markers of hypochromia rather than microcytosis) may correlate better with severity of IDA than MCV[223]. Current guidelines state that MCV alone is not enough to make a diagnosis of IDA and other parameters, namely ferritin, should be used to assess iron status[222] as ferritin correlates well with total body iron stores and is a better marker of iron deficiency; low MCV occurs only in the later stages of iron deficiency[224]. Data on ferritin was not available for all the patients in our group, and MCV was used in this study due to its widespread use and availability. Both markers are less reliable in elderly and/or hospitalized patient populations several other comorbidities e.g. inflammation and anemia of chronic disease[225] but may be more reliable in the younger group that overall has a lower rate of comorbidities.

7.5 Conclusion

There is a lack of data on the outcomes for patients with unexplained IDA, and existing studies imply that the current management of IDA alone is often incomplete or inadequate[226]. This study has attempted to address some of these gaps so as to improve patient care. In patients ≤50 years old presenting with IDA, the overall diagnostic yield of CE for significant SB findings was 32.3%. Around 5% were diagnosed with SB neoplasia. In this cohort, lower MCV and weight loss were associated with higher risk of a diagnosis of significant SB neoplasia findings. Therefore, in young patients with certain clinical features such as low MCV and weight loss, some form of SB imaging such as CE should be prioritised.

Chapter 8 Effect of CE image visualisation quality on diagnostic certainty

As established in the earlier chapters of this thesis, CE is at present an entirely visual diagnostic tool which is highly reliant on image quality. This chapter therefore aims to investigate how image quality affects diagnostic certainty for CE readers.

8.1 Introduction

Image quality is in itself dependent on several factors ranging from hardware (camera ability), software (image processing ability) and patient factors including bowel preparation and gut motility. However, although there is a paucity of evidence by way of peer-reviewed studies, it is perhaps intuitive that optimising visualisation quality should have a positive effect on diagnostic accuracy and certainty.

Previous work has been limited by the lack of a widely-accepted method for quantifying visualisation quality in CE reporting. A few studies have been carried out attempting to standardise the grading of SB preparation and to establish a universal grading score, but none so far have been widely adopted in clinical practice[193]. Efforts have also been limited by the wide variety of proprietary capsule reading/reporting software on the market, which hampers attempts at standardisation.

In this study, the contribution of various image parameters to visualisation quality and their effect on certainty of diagnosis of small bowel lesions is examined. The use of image parameters may aid standardisation in the reporting of small bowel visualisation quality as these general parameters are common across image processing, transcending the range of proprietary software.

8.2 Methods

8.2.1 Phase 1: initial pilot study

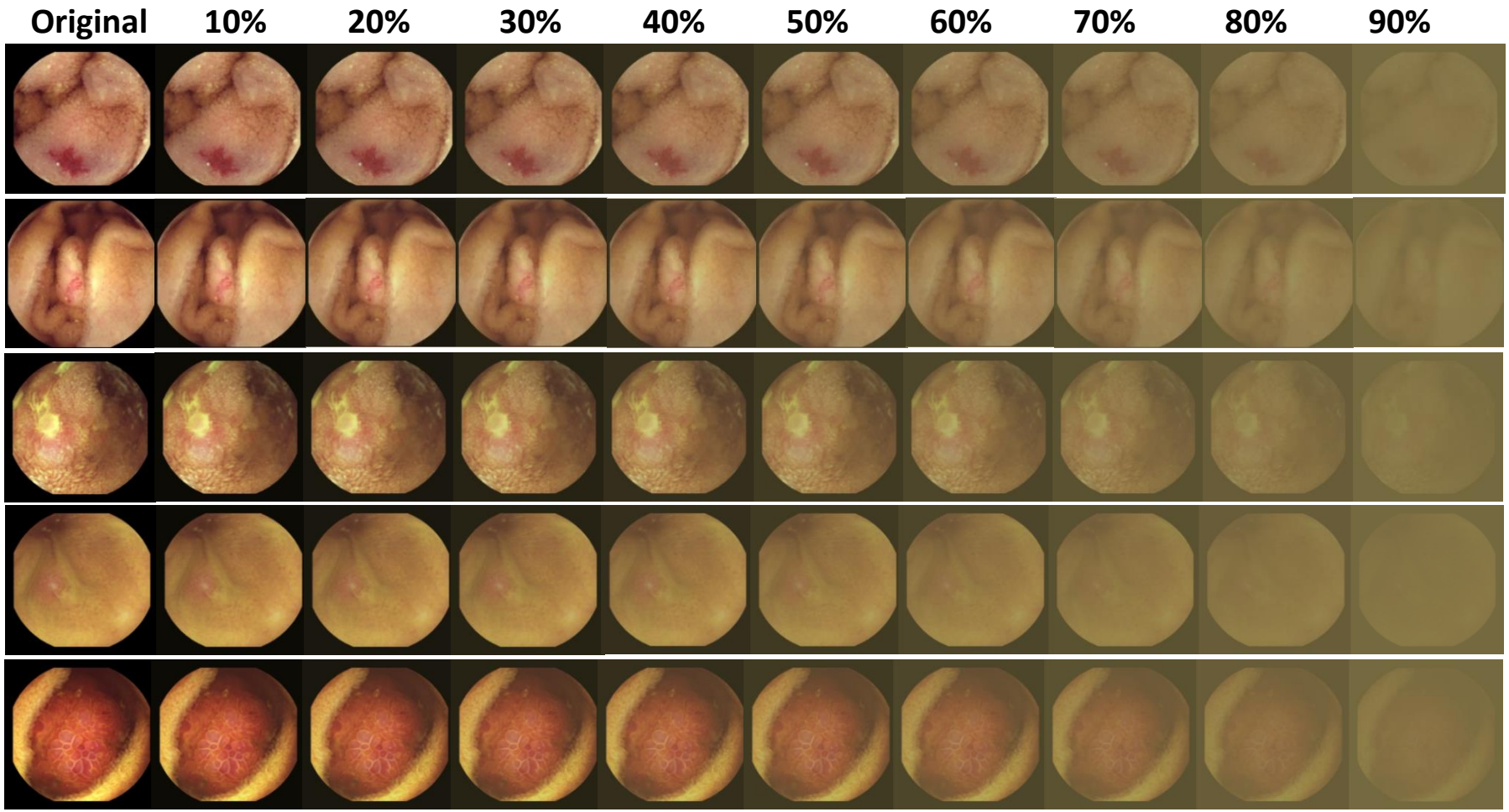
The initial pilot study aimed to identify parameter thresholds or landmarks at which CE images became inadequate for diagnostic purposes. Five clear CE images of common SB pathology were selected: a P1 angioectasia, P2 angioectasia[93], ulcer, aphtha and malignant polyp (as a representative of neoplastic lesions). These images were deemed "clear" and unambiguous by two expert CE reviewers at our centre, and standardised to a resolution of 320x320 pixels (px). Each image was processed for 3 parameters using GIMP2 image processing software, an open-source graphics editor compatible with several operating systems and image formats (www.gimp.org):

(1) Opacity: The colour of the mask filter was colour-matched to that of luminal content from a clearly poorly-prepared CE video, to simulate the effects of large amounts of luminal debris. 9 processed images were obtained using colour masks overlying the original "clear" image, set at opacities of 10-90% in 10% increments.
(2) Blurriness: A Gaussian blur was chosen to simulate the effects of movement, therefore approximating both poor focus and the effects of rapid movement of the capsule through the bowel. 9 processed images were obtained using blur radius 1-10px in 1px increments.
(3) Contrast: Contrast was chosen as a parameter as this adjustment is common across most commercial capsule reporting software. Images were processed from -50% contrast to +50% in 10% increments. The images obtained are shown in **Figure 8.1**.

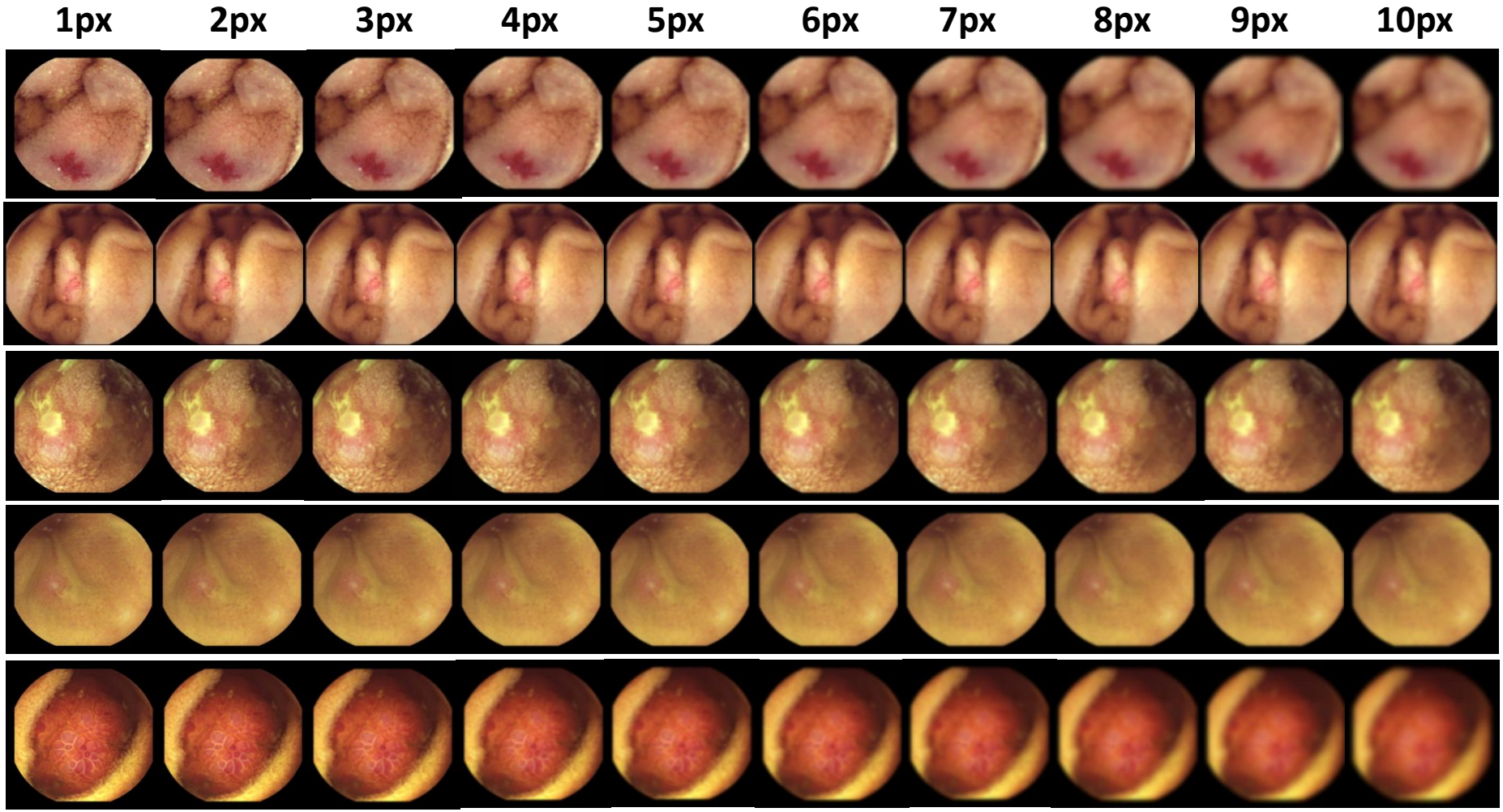
The sheer number of images resulting from this systematic stepwise image modification, even with only five original images, was the reason for an initial pilot study. A smaller group of reviewers was recruited compared to the second phase, as each reviewer had to agree to sift through this large number of images generated, whereas the second phase would focus on a wider range of reviewers and also of different images of SB pathology.

Figure 8.1: Panels showing range of images used for pilot study. (a) Opacity; (b) Blur radius; (c) Contrast

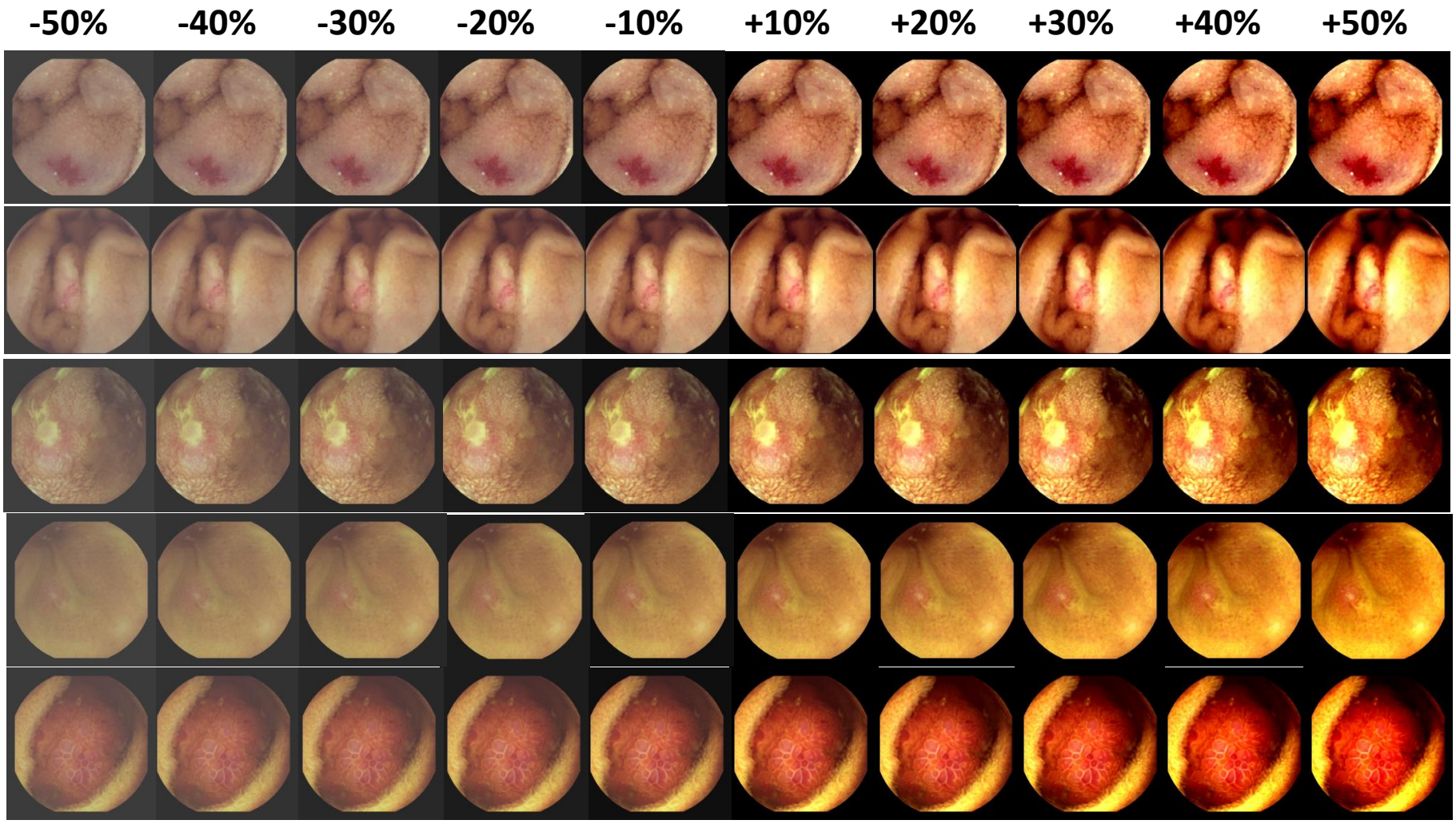
(a) Image set, with original images, altered for increasing opacity



(b) Image set altered for increasing blur radius



(c) Image set altered for decreasing and increasing contrast



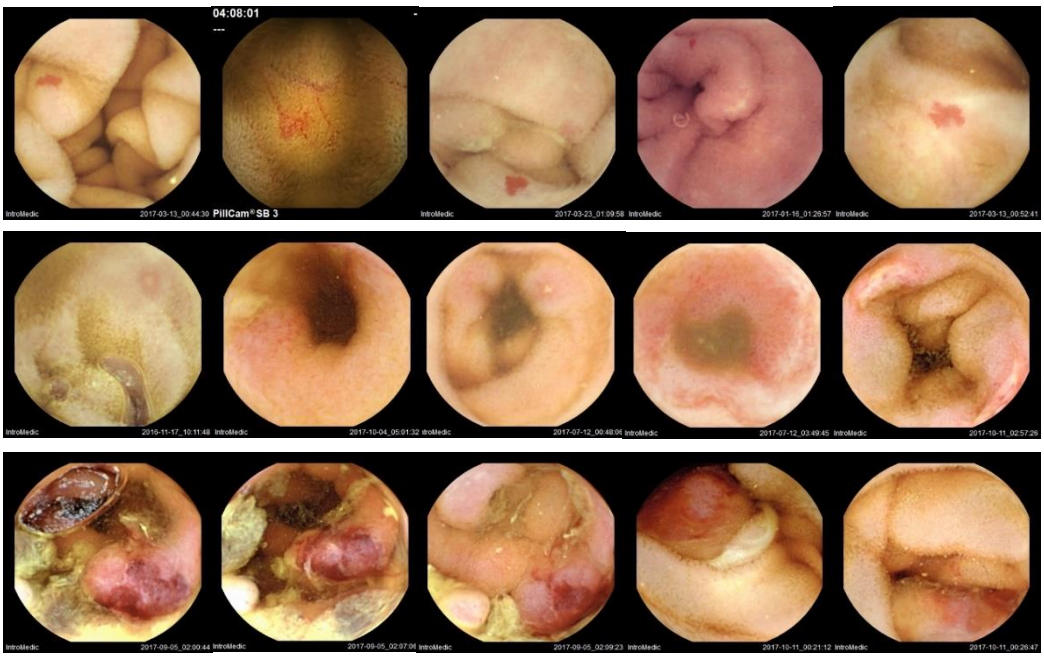
A group of 9 expert readers from several centres were then asked to review the resulting set of 9 original and 190 processed images, which were presented to them in random order using an online survey platform. For each image, reviewers were asked to evaluate whether it was adequate (or not) for diagnostic purposes, i.e. from the image, could they be sure of the diagnosis. Based on the percentage of reviewers deeming each image adequate or otherwise, four points where perception of image quality changed significantly were determined for each parameter. **Appendix III** shows the online survey platform which was used to gather data for this phase of the study.

8.2.2 Phase 2: Validation

Common SB lesions were classified into three main types: vascular, inflammatory and neoplastic/possibly malignant. Therefore three further sets of 9 clear images each were obtained; all these images were deemed "acceptable" by the same two expert CE readers as above. The images of vascular lesions were obtained from the same set as used in a recent study by Leenhardt *et al*, who have established an expert consensus on the nomenclature of vascular lesions seen on SBCE[227]; this was an additional step to ensure that the starting images for this phase of the study had already been deemed "clear" by a group of expert CE readers based across multiple centres.

Based on the findings of the pilot study, each of the images in this new set was processed for 4 points per parameter as above. This resulted in a second set of 27 original and 108 adjusted images, some of which are detailed in **Figure 8.2**. 20 experienced-expert CE readers reviewed the resulting images using an identical setup to the first phase. Results from each group of images (i.e. each type of pathology) were pooled and the mean percentages of readers finding each image adequate, with standard deviations (SD), were used to examine results. **Appendix IV** details the experience of the CE readers involved.

Figure 8.2: Examples of the original images used in Phase 2. Top row: vascular lesions; middle row: inflammatory lesions; bottom row: neoplastic lesions



8.3 Results

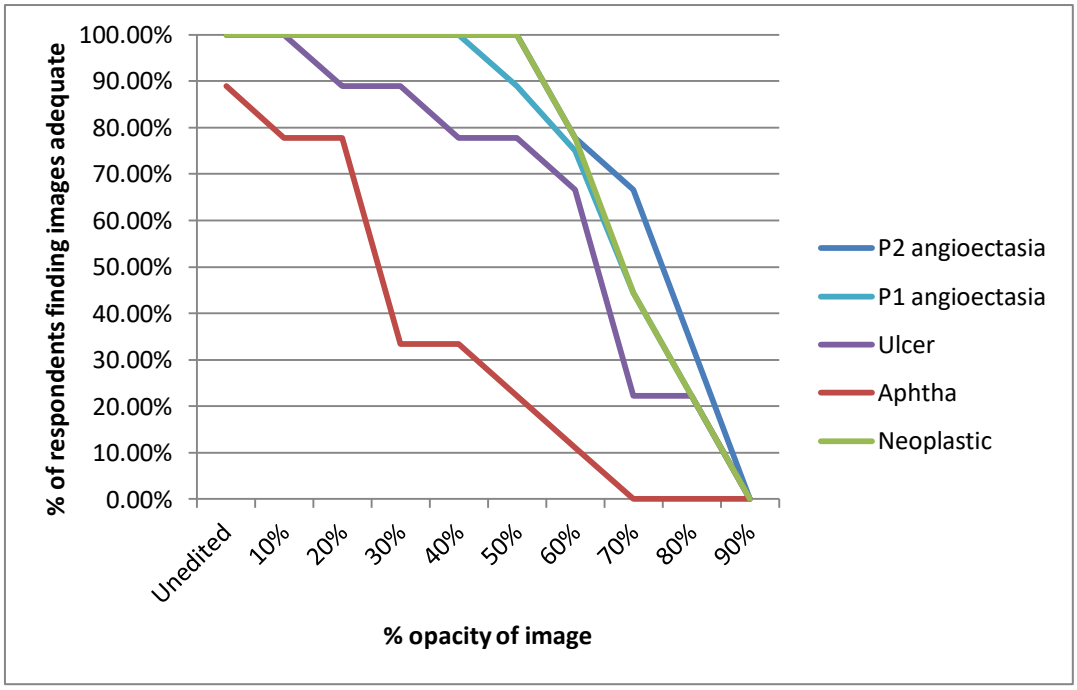
8.3.1 Phase 1: Pilot study

For image opacity, both angioectasias and the neoplastic lesion were considered adequately visualised below 40% opacity whereas the threshold was lower for both the ulcer and aphtha (10% opacity). Increasing blur radius significantly impacted the acceptability of images for reaching a diagnosis with confidence; for most images, blur radius 3px was the threshold for adequate visualisation but even 1px of blur radius decreased the visualisation quality of the aphtha image. The aphtha image was also affected the most by decreased contrast; conversely the ulcer was deemed more inadequately visualised with higher contrast. The other images were generally adequately visualised at ±10% contrast.

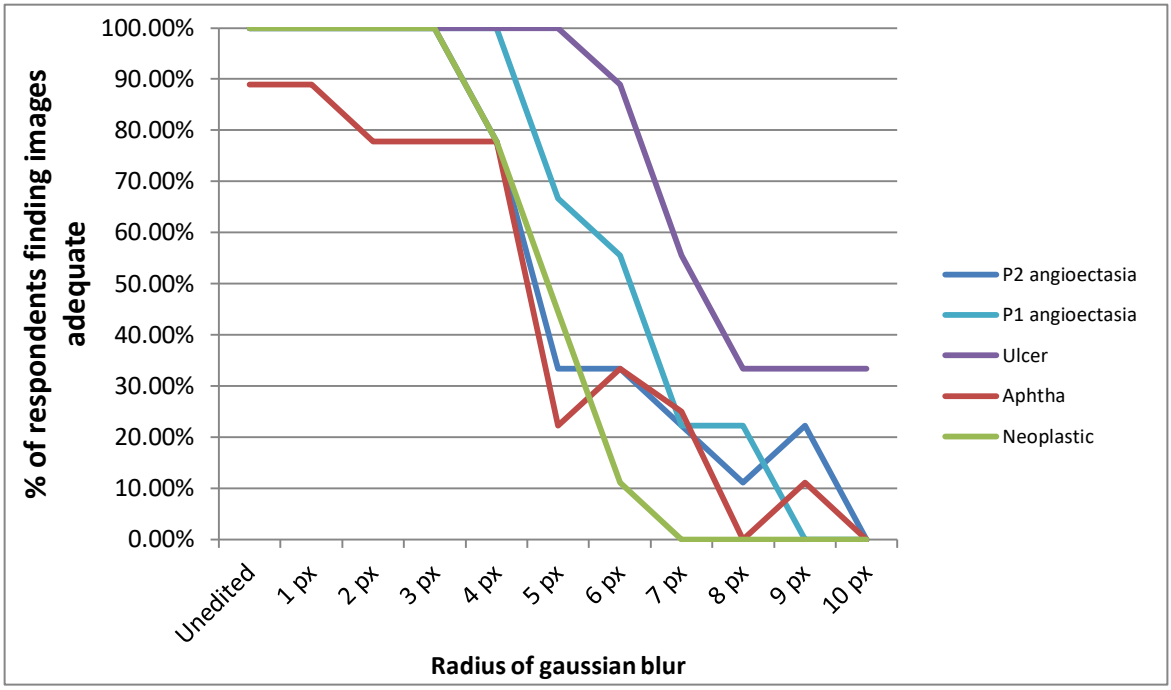
Figure 8.3 shows the percentage of expert CE readers who found each image adequate for diagnostic purposes, for each of the parameters examined.

Figure 8.3: Percentage of readers who found each image diagnostically adequate. (a) Opacity; (b) Blur radius; (c) Contrast

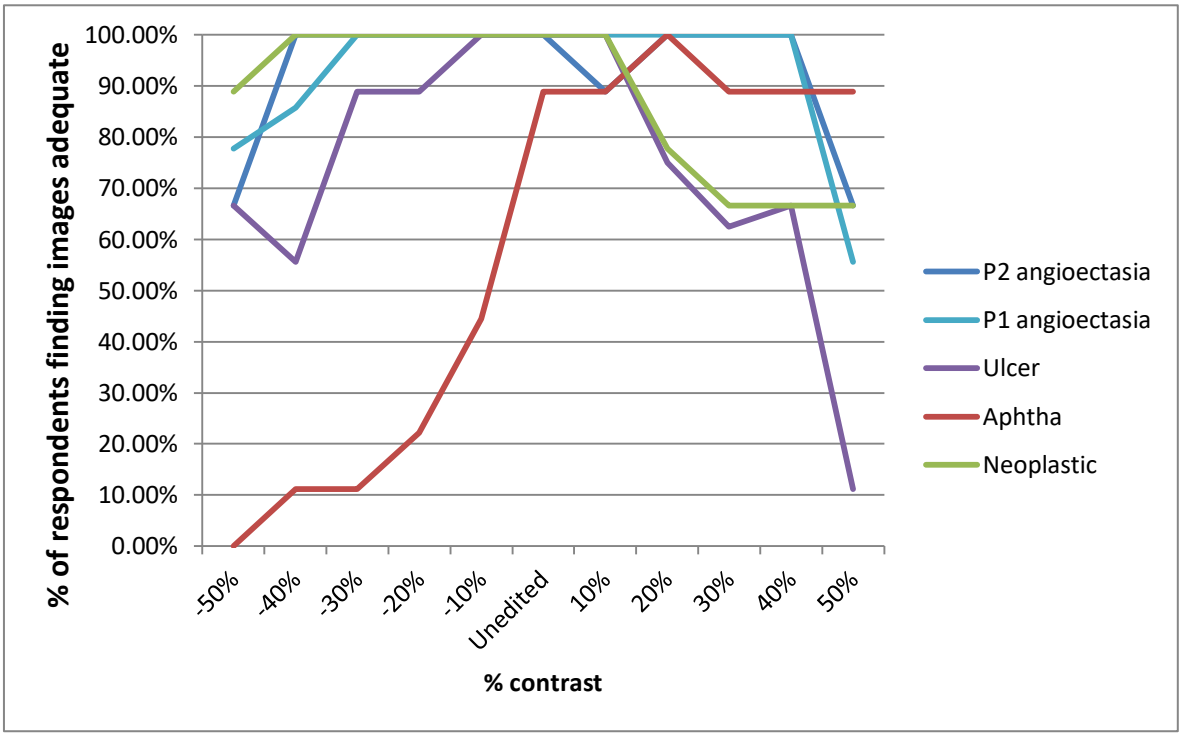
(a)



(b)


100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
% of respondents finding images adequate
Unedited
1 px
2 px
3 px
4 px
5 px
6 px
7 px
8 px
9 px
10 px
Radius of gaussian blur
P2 angioectasia
P1 angioectasia
Ulcer
Aphtha
Neoplastic

(c)


100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
% of respondents finding images adequate
-50%
-40%
-30%
-20%
-10%
Unedited
10%
20%
30%
40%
50%
% contrast
P2 angioectasia
P1 angioectasia
Ulcer
Aphtha
Neoplastic

8.3.2 Phase 2: Validation of results from pilot study

In vascular and inflammatory lesions, diagnostic certainty was least affected by increasing image opacity, requiring opacities >90% before most readers considered images inadequate for diagnosis. The greatest negative effects of image opacity were seen in neoplastic lesions where significantly fewer readers found images adequate at >50% opacity. In general, the spread of responses as demonstrated by the error bars in the images in **Figure 8.4** as well as standard deviations in **Table 8.1** was greater for both vascular and inflammatory lesions compared to neoplastic ones.

Similar results were obtained with increasing blur radius, simulating the effects of motion blur from segments of rapid small bowel transit and poor focus. The proportions of readers finding vascular and inflammatory images adequate for diagnosis did not drop significantly at wider blur radii, while the proportion who found images of malignancies diagnostically adequate dropped at blur radius 6px. Once again, the spread of responses was greatest in the set of vascular lesions and responses were most cohesive for neoplastic lesions.

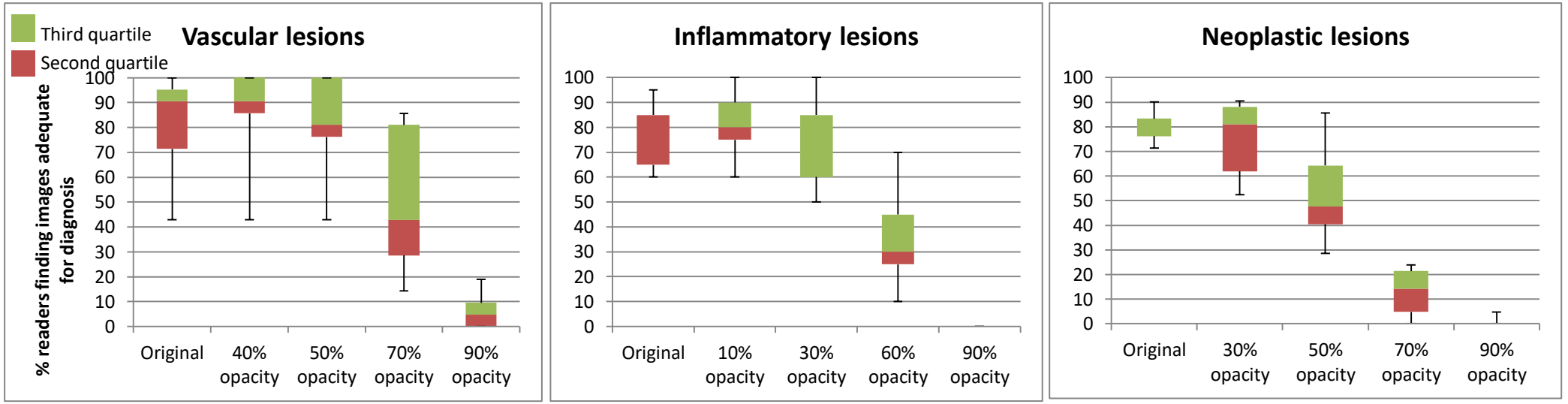
Decreasing contrast had greater negative effect than raised contrast, most obvious in the set of neoplastic lesions. Responses from the group of reviewers were markedly less cohesive for vascular lesions compared to inflammatory and neoplastic ones.

Table 8.1: Mean±SD of the percentage of reviewers who found images in each type of pathology adequate for diagnostic purposes

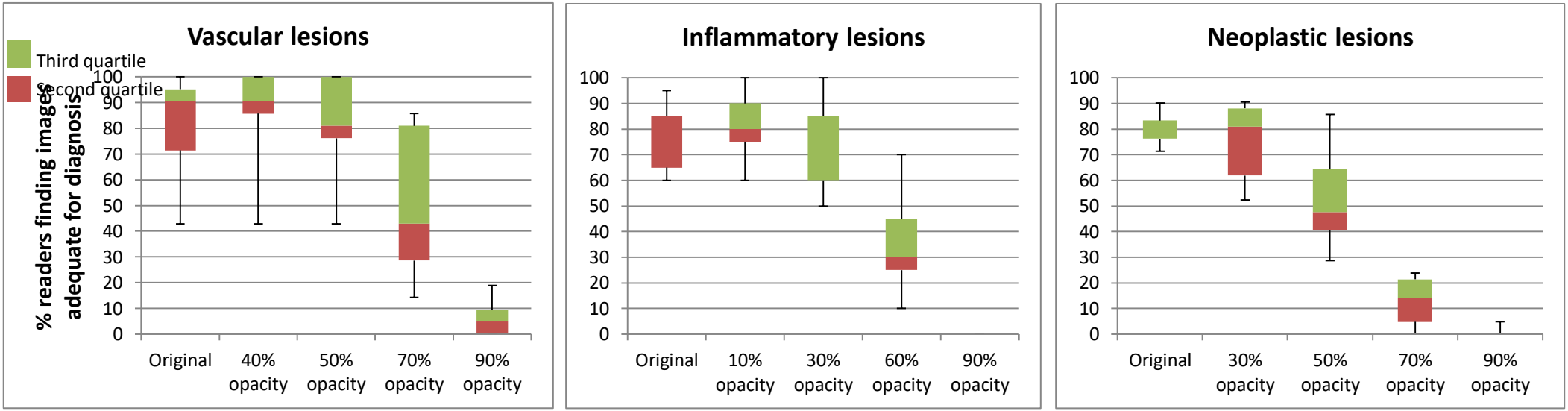
Lesion type/ Parameter					
OPACITY	**Original**				
Vascular lesions	84.1±18.9	40% opacity: 84.7±20.6	50% opacity: 79.9±22.0	70% opacity: 51.9±30.0	90% opacity: 6.3±7.1
Inflammatory lesions	79.4±13.1	10% opacity: 82.2±14.2	30% opacity: 70.0±17.5	60% opacity: 33.9±18.5	90% opacity: 0±0
Neoplastic lesions	79.5±6.5	30% opacity: 74.8±15.7	50% opacity: 53.1±19.9	70% opacity: 12.9±9.8	90% opacity: 0.7±1.8
BLUR RADIUS	**Original**				
Vascular lesions	84.1±18.9	3px: 90.0±20.2	4px: 77.8±22.1	7px: 49.7±26.2	9px: 33.9±22.6
Inflammatory lesions	79.4±13.1	2px: 85.0±11.2	3px: 78.3±7.9	5px: 62.2±12.3	8px: 35.0±16.8
Neoplastic lesions	79.5±6.5	3px: 70.1±10.2	6px: 41.5±9.4	7px: 40.0±6.6	9px: 19.7±6.4
CONTRAST	**Original**				
Vascular lesions	84.1±18.9	-50% contrast: 61.9±30.3	-30% contrast: 80.4±24.5	+20% contrast: 87.8±11.7	+50% contrast: 49.7±33.6
Inflammatory lesions	79.4±13.1	-50% contrast: 46.7±19.2	-20% contrast: 76.7±13.5	+30% contrast: 62.8±19.4	+50% contrast: 33.3±20.3
Neoplastic lesions	79.5±6.5	-50% contrast: 38.1±16.7	-30% contrast: 63.3±17.3	+20% contrast: 82.3±9.8	+50% contrast: 56.5±14.7

Figure 8.4: Effects of altering image parameters in Phase 2, shown as median and spread of responses for each set of images. (a) Opacity; (b) Blur radius; (c) Contrast

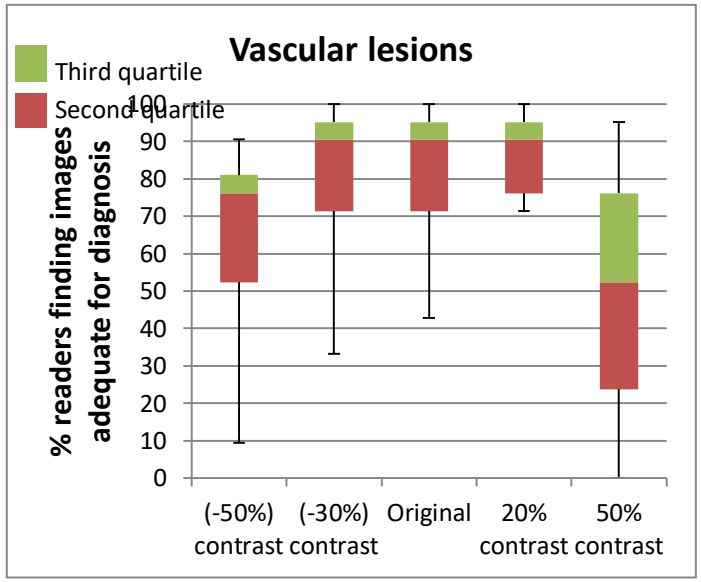
(a) Effect of increasing image opacity

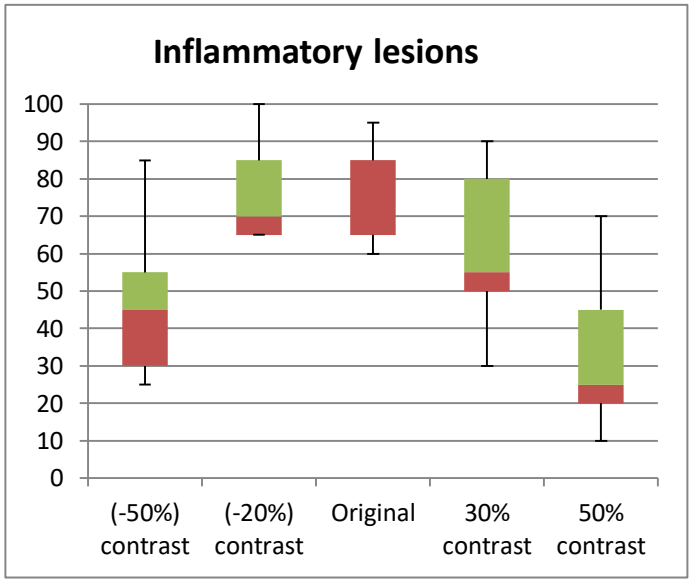


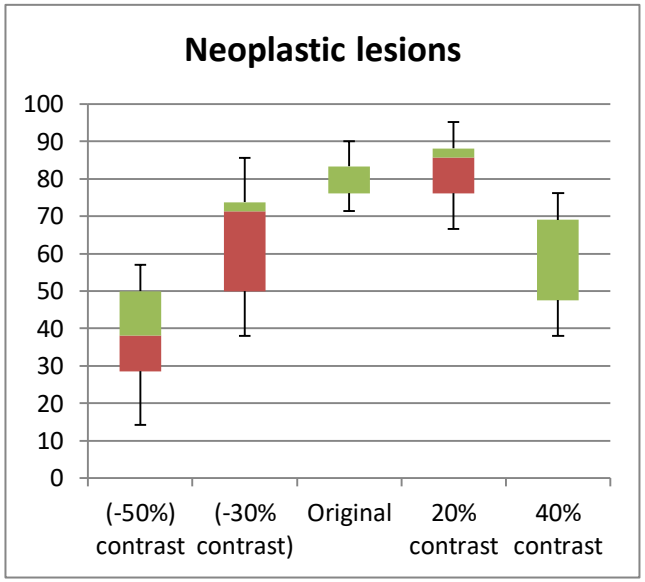
(b) Effect of increasing blur radius



(c) Effect of altering contrast







8.4 Discussion

8.4.1 Effect of image parameters on CE image quality

Current CE guidelines recommend that image quality is recorded when reporting CE[21]. At present however there are few validated scales which have been developed to quantify image quality in CE. Furthermore, these scales are not in wide use and have not been subjected to more widespread testing and adoption; they also tend to be based on subjective parameters[193,228]. This creates discrepancy and a degree of uncertainty when reporting CE, for both clinical and research purposes.

Image quality is affected not only by luminal conditions but also the hardware of CE systems themselves. The majority of available literature concentrates on quality of bowel preparation[229,230], perhaps because clinicians have some control over these factors. At present, there is little which examines the effect of hardware or software on image visualisation in the clinical or real-world context. Nevertheless, it is important for technology to be developed with the end-user in mind. Much of current CE image-processing technology is developed by the manufacturers and then tested by clinicians; involving clinicians in the development process could well be more efficient and effective.

A few studies exist pitting different capsule models against each other, to assess the effects of hardware and software improvements. A 2016 study by Monteiro *et al* compared the PillCam® SB2 to SB3, finding that the improved image resolution and faster variable frame rate increased duodenal papilla detection rates from 24% to 42.7%[231]. Kim *et al* in 2018 compared the PillCam® to Mirocam[232]. A small group of patients underwent simultaneous 2-capsule CE. Capsule reviewers achieved an agreement rate of 70%, implying that just under a third of patients had different findings between the two models of capsule. In another study by Omori *et al*, the use of the 3rd-generation PillCam® SB3 was found to reduce time burden for both expert and inexperienced readers. The authors propose that this was due to an improved software algorithm for adaptive frame rate and improved image resolution[233].

8.4.2 Implications of results for further developments

Therefore, this study represents a conscious attempt to "work backwards", starting from images deemed adequate by expert CE readers and adjusting them in a stepwise manner until a point where the majority of readers felt these images were inadequate for diagnostic purposes. The results show that image sharpness may have more effect than opacity, especially in the diagnosis of potentially malignant small bowel lesions. A relatively high level of image opacity was "tolerated" by the group of CE readers in this study whereas blurriness seems to have a greater impact on visualisation quality and reviewer confidence in the diagnosis. Furthermore, there was greater agreement amongst the reviewers about overall image quality in the neoplastic images compared to vascular lesions.

In combination with the aforementioned studies, this implies that software algorithms (such as adaptive frame rate) and hardware improvements (such as camera resolution) which are able to obtain more and sharper images, despite variations in bowel motility, would help to provide capsule readers with better quality images and aid diagnosis. Software which is able to adjust images already obtained, e.g. by sharpening images or adjusting contrast to improve visualisation, could also be of use. Increased diagnostic certainty based on higher-quality capsule images could reduce reading time and therefore burden on capsule readers; higher quality images could further improve the development of and confidence in computer-aided diagnostic software. Interestingly, at present there is no "zoom" function available in CE – this is perhaps an area for further development and study.

Currently, existing attempts to develop computer-based automated bowel preparation grading systems have been based mainly on the overall colour of frames[228] or on the percentage of the lumen which has been obscured by debris and bubbles[194,234,235]. These approaches can work well for approximating bowel segments or detecting gross abnormalities such as blood in the lumen[236], but do not take into account the effect of image sharpness and motion blur. Furthermore, the results of this study suggest that the quality of bowel preparation which can be tolerated differs according to clinical indication for the CE examination. For instance, CE carried out for suspected small bowel bleeding may not require as pristine a bowel lumen as one looking for the lesions of mucosal inflammation or subtle small bowel tumours. This appears to be the first study which specifically examines the effect of image visualisation quality on different types of small bowel pathology.

8.4.3 Limitations

Limitations of this study are, firstly, related to the lack of existing data or previous work for comparison. Furthermore, the data set comprises only still frames, with a relatively limited sample size owing to the need to recruit expert CE readers and for them to critically scrutinise a large set of images. Fewer data points for each parameter were included in the second phase, using four points for each image rather than the more detailed stepwise adjustments made in the first, pilot phase, in order to allow for a wider range of images to be examined.

8.5 Conclusion

In this study, poor visualisation quality in the parameters examined – luminal opacity, blurriness and contrast – had the greatest effect on diagnostic certainty of malignant lesions. Therefore, this implies that software to increase contrast and sharpen images or correct for poor focus can be used and developed to improve visualisation quality; smart frame rate adaptation could also improve the number of high-quality frames obtained even with variations in bowel motility and transit times. Furthermore, the thoroughness of SB preparation is most important when CE is being carried out for suspected SB malignancy – greater care should be taken to obtain high-quality images for this indication.

Future applications of this data include the potential integration of the parameters investigated here with computer-assisted CE diagnostic or bowel preparation grading software. Further studies could also examine the effects of bowel visualisation quality in colon CE; the contribution of image quality to diagnostic accuracy and certainty may be even greater in colon CE due to the increasing amounts of debris in the distal gastrointestinal tract, where one of the main indications of colon CE is to detect colonic malignancies.

Chapter 9 Discussion and conclusions

9.1 Summary and overall conclusions

In this thesis, I have shown that:

- Digital image-enhancement methods such as FICE are marginally useful for improving visualisation quality of capsule images; however their overall clinical impact and utility is limited.
- Image selection methods such as SBI are of value in digitally identifying areas of GI bleeding prior to review and therefore reducing CE reading times. This does not compromise on diagnostic accuracy in the setting of GI bleeding and is especially useful in patients with active GI bleeding at time of CE.
- The use of laxative bowel preparation improves visualisation quality of CE images but has not been shown to have an appreciable effect on diagnostic yield or completion rate of CE examination.
- Optimising CE image visualisation quality improves diagnostic certainty. Improved image visualisation quality has the greatest effect when examining images of neoplastic, potentially malignant SB lesions (compared to vascular and inflammatory-type lesions).
- CE is useful in the acute to semi-acute setting to triage and diagnose patients with suspected SBB, i.e. those presenting with IDA and/or melaena, negative upper GI endoscopy and no convincing signs of large bowel pathology. The early use of CE following negative initial upper GI endoscopy has the potential to defer colonoscopy in order to take pressure off overburdened systems and reduce the overall number of colonoscopies performed in such patients.
- Younger patients (age <50 years) presenting with IDA and who have undergone negative bidirectional endoscopies should be particularly considered for early/expedited CE as they are more likely to have significant SB pathology, especially in the context of low MCV and weight loss as a presenting symptom.

9.2 Discussion

GI bleeding, and especially overt or suspected SBB, remains the main clinical indication for CE in routine practice. CE has been shown to be a useful diagnostic tool for the aforementioned reasons discussed in this body of work; however, the data presented here also suggests that it could potentially have a greater role in the semi-acute setting due to its ease in use, minimal invasiveness, and lesser requirement for manpower compared to conventional GI endoscopy.

Certainly, CE has the potential to be used as a screening tool in patients presenting with suspected SBB, following negative UGIE and before proceeding to colonoscopy – such an approach could optimise resource use by triaging patients who should (or need not) undergo urgent inpatient colonoscopy, cutting costs incurred from unnecessary investigations, lengthy hospital stays, and sparing a proportion of patients a more invasive, unpleasant procedure.

SBI software has been shown to be reliable for the identification of active GI bleeding and can be used to speed up the reporting process in this setting. On the other hand, FICE technology requires further development in order to be clinically useful – or perhaps the use of FICE is not the solution here, and other methods of image enhancement and selection should be pursued in future work. Overall, however, digital methods of image enhancement are only as good as the hardware allows. Future improvements to CE systems should ideally centre on improving hardware quality. Colour alteration with software such as FICE, blue mode and ALICE does not seem to be as useful for image delineation or diagnosis, whereas improved focus and image resolution do appear to improve diagnostic certainty.

Where there is clinical suspicion of other non-vascular causes of GI bleeding such as SB tumours, more finesse is indicated in order to improve the diagnostic capability of CE investigation. In current clinical practice, the most reliable and controllable method to enhance visualisation quality is to use laxative bowel preparation. However, apart from patient condition and tolerance, the use of bowel preparation should also be influenced by the indication for CE examination, for example, considering whether the potential source of GI bleed is vascular, inflammatory or malignant.

The data here suggest that the diagnostic certainty for neoplastic-appearing lesions is most affected by poor visualisation quality, compared to the other common “classes” of SB pathology. Even though the use of laxative bowel preparation improves visualisation quality

as perceived subjectively by CE readers, the effect on diagnostic yield is minimal. This implies that the value of using laxative bowel preparation lies in lesion delineation and the identification of pathology. Therefore, rather than focusing on achieving a pristine bowel in all patients undergoing CE, greater attention to bowel preparation should be given to patients suspected of having a malignancy or other neoplastic lesion, and conversely, the need for bowel preparation should also not hold up a (semi-)urgent capsule in a patient who is likely to have vascular lesions causing SBB. Other factors which can influence lesion detection and diagnostic certainty should be taken into account and certainly warrant further investigation; these include individual reviewers' reading technique, capsule model and technology with their effects on image quality, as well as the use of repeat or "second look" capsule examination.

A significant body of previous work has established that advancing age is correlated to the incidence of vascular lesions, whereas it has been shown here that younger patients are more likely to have significant SB findings on CE. Other factors found to be predictive of significant findings are the presence of weight loss and lower MCV as a marker of iron deficiency – taken together, these are factors which should prompt a more urgent referral in the young patient presenting with IDA.

9.3 Limitations

The specific limitations of each individual study have been discussed in the relevant chapters. As a whole, however, this work is perhaps mostly limited by the relatively small size of the field and similarly small amount of data available. As previously discussed, CE examinations are labour-intensive to read and interpret, therefore data collection for studies is equally as time consuming and labour intensive. In order to reach meaningful sample sizes, many of the studies making up this work had to be meta-analyses, i.e. building on existing data, retrospective in design so as to make use of data gathered over years to decades, and/or multicentre in nature.

The use of data from several centres means there was inevitable heterogeneity between capsule readers at the various centres from which data were collected. Furthermore, there remains no standardised reading and reporting framework for CE, making this heterogeneity between individual readers and centres all the more obvious. In this work, I have attempted to address this limitation by conducting sensitivity and heterogeneity analyses in the meta-

analyses, and by recruiting from a group of fairly similar-level expert capsule readers; however it must be acknowledged that these drawbacks remain and are fairly significant.

Data collected over longer periods of time is also subject to intra-observer variation stemming from the learning curves of the capsule readers involved. In addition, capsule technology has improved over time and, as shown in this work, improved visualisation quality can improve diagnostic certainty and clarity. I have attempted to address this potential source of heterogeneity by prudent definition of data collection periods when collecting retrospective data from previous capsule examinations. For example, data collection for the multicentre study in Chapters 7 used only capsules carried out over a 5-year period from 2010-2015 in order to capture a group of capsules which had been reported by expert readers already established and experienced in the field by this period of time. Similarly, the study in Chapter 6, based at our tertiary care centre, excluded data from the earliest capsule models such as PillCam®M2A, so as not to include data from capsule models with poorer image quality.

9.4 Implications for practice

In routine/everyday clinical practice, the following suggestions are therefore offered to optimise the use of CE in patients presenting with GI bleeding and to streamline their management:

- In patients presenting with melaena and/or IDA, negative UGIE and in whom there are no symptoms suggestive of colonic pathology (such as frank rectal bleeding, diarrhoea or abdominal pain), an urgent CE is of diagnostic value and can be used as a triage tool.
- Young patients aged 50 years old and below who present with isolated IDA and negative bidirectional endoscopies should be referred more promptly for CE to investigate the SB as SB findings in these patients are more likely to be clinically significant and require timely intervention.
- The indications for CE and differential diagnoses should be evaluated on an individual patient basis when deciding on the mode of bowel preparation. In patients where there is a higher clinical suspicion of vascular causes of bleeding – or frank bleeding such as melaena – laxative bowel preparation may not be as vital; rather, the focus should be on expediting CE in order to better identify active bleeds and the location

of bleeding lesions in the GI tract. Conversely if pathologies such as IBD or malignancies are suspected to be the cause of GI blood loss, closer attention should be paid to achieving clear views.

- When reading and reporting a CE examination, SBI frame-selection software is of particular value in locating frames where active bleeding is seen and is therefore useful to speed up CE reading in the acute to semi-acute setting.
- Conversely, image enhancement software such as FICE is of limited utility, although it may potentially improve the visualisation of bleeding lesions.

9.5 Directions for future development

Based on the results presented in this work, the efficient, judicious use of CE as a diagnostic tool is a major factor contributing to its clinical utility in patients presenting with GI bleeding. Future developments which could improve its utility include, firstly, an emphasis on hardware which will allow improved image resolution and focus, i.e. to improve image quality and therefore diagnostic certainty.

Building on the limitations of this work, it has certainly highlighted that much can be done to standardise CE reading and reporting, both for research and clinical purposes. Recently, Leenhardt *et al* have attempted to develop a structured terminology for capsule reading and reporting, starting with a Delphi consensus on the definition of vascular lesions[227] and have now expended this work to include inflammatory lesions (this data remains under review at time of writing). There is also the need for training guidelines and competency frameworks for capsule reading, to ensure that qualified CE readers have attained a minimum standard. Previous work has already shown that not only clinicians, but nurses and clinical scientists can do just as well in capsule reading and reporting[237]. Structured reporting and competency frameworks can ensure that capsule reporting is more consistent and homogeneous than it currently is, allowing a wider range of staff to read and report capsule examinations and therefore even freeing up doctors to make clinical decisions such as formulating and enacting management plans[238]. At present, there is only one structured capsule reading competency evaluation, developed by the Mayo Clinic[239]; this has yet to be fully validated in a wider group of readers, let alone widely adopted.

Perhaps the area with the greatest potential for development however is the field of artificial intelligence including machine learning algorithms and computer based or aided diagnosis.

These methods offer much potential to improve the efficiency of capsule examination, which remains limited by reading times, human factors and manpower requirements. Currently, the main approach adopted is to feed endoscopic images of certain types of pathology to various types of artificial neural networks, in order to train these networks to recognise the pathology of interest. Work has already emerged examining the use of such networks in conventional endoscopy, to identify colonic polyps[63] and upper GI tract cancers[240]. In the context of CE, such studies have mainly focused on the identification of angioectasias[241,242], and the body of data remains small. The main methods which have been used to identify regions or areas of interest include image segmentation and colour/pixel recognition - similar to the technology employed in the SBI. However at the present time these methods remain rudimentary and mostly image-based, working from still frames. Much further work needs to be done so that these techniques can be applied to long segments of video, as well as to establish their reliability.

Overall, CE has proven to be a versatile mode of minimally-invasive GI investigation with much potential for several new indications. This thesis has attempted to establish ways in which the use of CE can be optimised so as to increase its clinical value, both within the limits of current technology and also to identify directions for future development.

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APPENDICES

I. Data collection forms sent to participating centres for the study in Chapter 7: Young patients referred for CE with isolated iron deficiency anaemia

II. Centres which contributed data towards the study on CE in young patients with iron deficiency anaemia

III. Example of the online survey platform used for the study in Chapter 8: investigating the parameters for visualisation quality in CE images

IV. Details on the experience of participating CE readers in the study on visualisation quality in CE images (Chapter 8)

V. Publication resulting from the work presented in Chapter 3: *Clinical validity of flexible spectral imaging color enhancement (FICE) in small-bowel capsule endoscopy: a systematic review and meta-analysis.*

VI. Publication resulting from the work presented in Chapter 4: *The validity of suspected blood indicator software in capsule endoscopy: a systematic review and meta-analysis.*

VII. Publication resulting from the work presented in Chapter 5: *Systematic review and meta-analysis: is bowel preparation still necessary in small bowel capsule endoscopy?*

VIII. Publication resulting from the work presented in Chapter 6: *Earlier use of capsule endoscopy in inpatients with melena or severe iron deficiency anemia reduces need for colonoscopy and shortens hospital stay.*

IX. Publication resulting from the work presented in Chapter 7: *Capsule endoscopy in young patients with iron deficiency anaemia and negative bidirectional gastrointestinal endoscopy.*

Appendix I **Data collection forms sent to participating centres for the study in Chapter 7: Young patients referred for CE with isolated iron deficiency anaemia**

CAPSULE ENDOSCOPY (CE) IN YOUNG IDA PATIENTS: Case Report Form (CRF)

Inclusion criteria: consecutive 19-50 years old patients undergoing CE for IDA.

Please fulfil one CRF for each included patient.

1. Center: _____

Physician filling in the CRF: _____

Date: _____

2. Patient's demographic data:

Gender (M/F): _____ Age:_____ Pts log number: _____

3. Patient's comorbidities

Cardiological (specify): _____

Renal: (specify): _____

Gastroenterological (specify): _____

Other (specify): _____

4. Associated signs/symptoms/family history

Significant weight loss (≥10% of initial body weight) o No o Yes

Family history (1st degree) of gastroenterological malignancy o No o Yes

Family history (1st degree) of small bowel malignancy o No o Yes

Previous history of malignancy o No o Yes (specify: _____)

History of renal failure: o No o Yes (specify: _____)

History of IBD: o No o Yes (specify: _____)

Presence of any other disease causing IDA: History of renal failure: o No o Yes (specify: _____)

Other (specify): _____

5. IDA history (before CE)

5a. Length of IDA history (time-interval between IDA diagnosis and CE (months): _____ (if less than 1 month (days): _____)

5b. At time of IDA diagnosis:

Hb level: _____ MCV: _____ Ferritin:_____ (Ferritin normal values: _____)

5c. Lowest Hb value reached: _____

6. IDA therapy (before CE)

6a. Patient received transfusions: o No o Yes (How many RBCU: _____)

6b. Patient received iron i.v.: o No o Yes (How many RBCU: _____)

- The i.v. therapy (including both transfusion and/or iron infusion) was:

  o Temporarily effective (Hb levels were restored with therapy and decreased after therapy cessation)

  o Not effective

6c. Patient received oral iron supplementation: o No o Yes

- If so: did the trial with oral iron fulfill BSG criteria ($FeSO^4$ 400 mg bid for at least 1 month and 3 months after anemia correction)? o No o Yes
- The oral supplementation was:

  o Temporarily effective (Hb levels were restored with therapy and decreased after therapy cessation)

  o Not effective

6d. Last values available before CE: Hb_____ date: _____

MCV :_____ date: _____

Ferritin: _____ date: _____

7. IDA work-up (before CE): evaluations performed

7a. Celiac disease (CD) serology or duodenal histology to rule out CD o No o Yes

7b. Haematological evaluation: o No o Yes

7c. Gynaecological evaluation (for pre-menopausal women): o No o Yes

7d. Faecal calprotectin: o No o Yes (if so specify level: _____)

7e. FOBT performed: o No o Yes

(if yes: when: _____ result: o positive o negative)

7f. Endoscopic evaluation before CE:

How many EGDs were performed: _____

How many colonoscopies were performed: ____ (how many were ileo-colonoscopies?: _____)

How many push enteroscopy were performed: _____

How many device-assisted enteroscopies were performed: _____

How many abdominal CT scan were performed: _____

How many CT- or MR-enterography were performed: _____

7f1. Last gastroscopy performed (date: _____)

o Negative

o Positive

Minor findings (findings not explaining reason for referral), please specify:

_____

_____

Major findings (potentially explaining reason for referral) , please specify:

_____

_____

If major findings were described on gastroscopy, please specify why the patient was referred for capsule endoscopy:

_____

7f2. Last colonoscopy performed (date: _____); with ileal intubation?

o No o Yes

o Negative

o Positive

Minor findings (not explaining reason for referral), please specify:

_____

_____

Major findings (potentially explaining reason for referral) , please specify:

_____

_____

If major findings were described on (ileo)colonoscopy, please specify why the patient was referred for capsule endoscopy:

_____

7f3. Radiological examinations performed (CT scan; CT- or MR-enterography); if positive please specify findings:

_____

7f4. PE or DAE performed: if positive please specify findings:

_____

8. Drug therapies (please report any therapy)

Drug	Dosage	Ongoing at time of CE?
		o Yes o No→o Stopped before CE (when _____)
		o Yes o No→o Stopped before CE (when _____)
		o Yes o No→o Stopped before CE (when _____)
		o Yes o No→o Stopped before CE (when _____)
		o Yes o No→o Stopped before CE (when _____)
		o Yes o No→o Stopped before CE (when _____)
		o Yes o No→o Stopped before CE (when _____)

8. Capsule endoscopy (CE)

Date: _____

Device used: □ PillCam SB1, □ PillCam SB2, □ PillCam SB3, □PillCam colon □ OMOM □ Olympus □ Mirocam □ Capsocam

Procedure: o Inpatient procedure o Outpatient procedure

Complete SB evaluation (caecum reached): o Yes o No

- Capsule remained in the stomach for all the recording-time
- Capsule stopped because of a stricture
- No reason explaining capsule slow transit
- Other (specify):

  _____

GTT: _____ SBTT: _____

SB toilette: o poor o fair o good o excellent

8a. Findings outside the small bowel (stomach/colon): o NO o YES

If YES please specify the finding and if this could explain the reason for referral:

_____

8b. SB findings; please specify each finding, estimated location, clinical value

	Finding	**Estimated location**	**Clinical value**
1	Vascular (_____) Inflammatory (_____) Mass (_____) Other: please specify_____	o Duodenum o jejunum o ileum	o P0 o P1 o P2
2	Vascular (_____) Inflammatory (_____) Mass (_____) Other: please specify_____	o Duodenum o jejunum o ileum	o P0 o P1 o P2
3	Vascular (_____) Inflammatory (_____) Mass (_____) Other: please specify_____	o Duodenum o jejunum o ileum	o P0 o P1 o P2
4	Vascular (_____) Inflammatory (_____) Mass (_____) Other: please specify_____	o Duodenum o jejunum o ileum	o P0 o P1 o P2
5	Vascular (_____) Inflammatory (_____) Mass (_____) Other: please specify_____	o Duodenum o jejunum o ileum	o P0 o P1 o P2
	Vascular (_____) Inflammatory (_____) Mass (_____) Other: please specify_____	Duodenum o jejunum o ileum	o P0 o P1 o P2

The CE video will be considered as POSITIVE if at least one P2 finding is described

9. CE complications

Aspiration in the airways: o NO o YES

Capsule retention (CE ≥15 days within the patient body): o NO o YES

CE excreted naturally without any therapy later than 15 days after ingestion:

o YES without any therapy/intervention (how many days after ingestion: _____)

o YES (how many days after ingestion: _____)after medical therapy (specify: _____)

o NO (please specify how was the capsule retrieved and when:

_____)

10. Management after CE

10a. Negative CE (normal CE or P0-1 lesions)

o Iron supplementation and follow-up

o Just clinical follow-up

o Gynecological evaluation/hematological evaluation

o Further small bowel evaluation (specify with which diagnostic tool: _____)

o Cessation of anticoagulant or anti-platelet agents

o Other (specify: _____)

10b. Positive CE (at least one P1 finding)

o Iron supplementation and follow-up

o Just clinical follow-up

o Gynecological evaluation/hematological evaluation

o Further small bowel evaluation (specify with which diagnostic tool and the final diagnosis:

_____)

o Cessation of anticoagulant or anti-platelet agents

o Other (specify: _____)

10c. Last visit (after CE)

Date: _____

Patient still anaemic? o NO o YES

Appendix II Centres which contributed data towards the study on CE in young patients with iron deficiency anaemia (i.e. Chapter 7)

France
Paris 6 University & APHP Hôpital Saint-Antoine, Paris

Greece
Hepatogastroenterology Unit, 2nd Dept of Internal Medicine - Propaedeutic, Research Institute and Diabetes Center, Medical School, National and Kapodistrian University of Athens, Attikon University General Hospital, Athens

Ireland
Department of Clinical Medicine, Trinity College Dublin, Dublin

Israel
Ha'Emek Medical Center, Afula
Sheba Medical Center, Tel Hashomer, and Sackler School of Medicine, Tel Aviv University, Tel Aviv

Italy
AOU Città della Salute e della Scienza di Torino, University of Turin, Turin
Catholic University of the Sacred Heart, Milan
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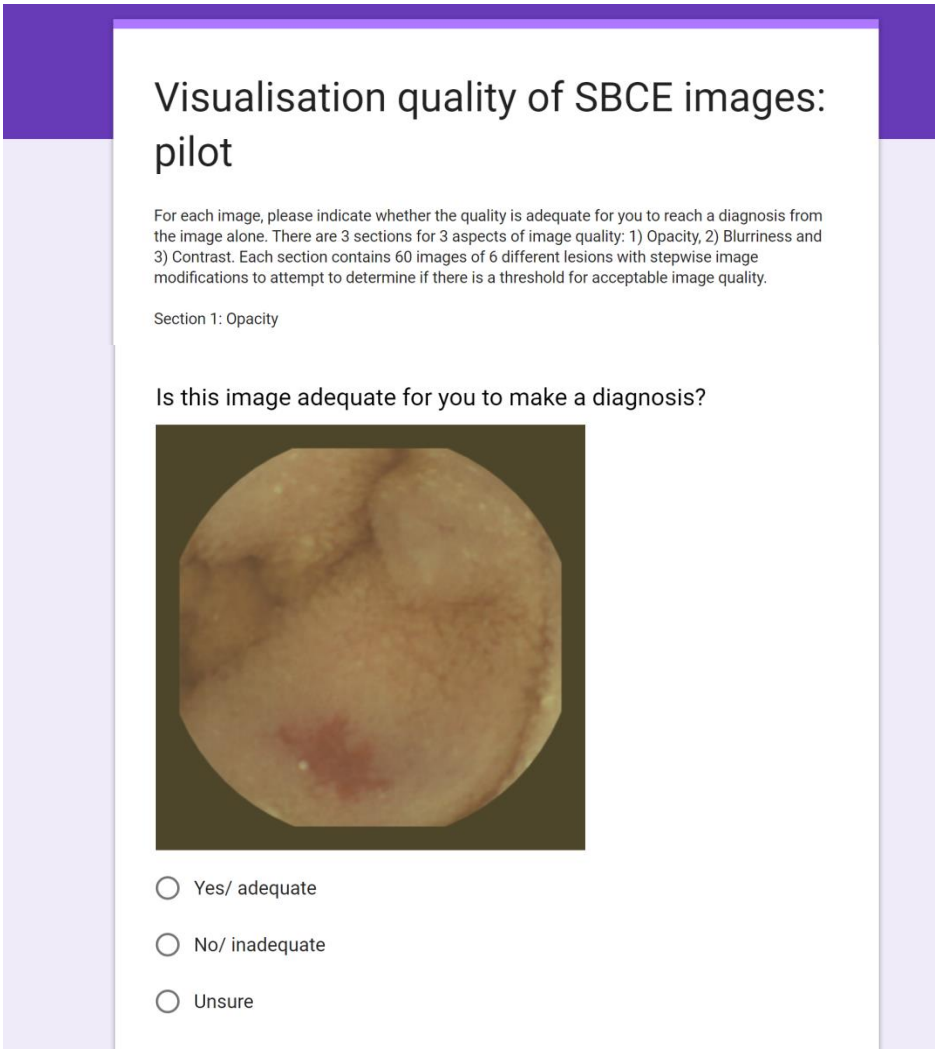
Spain
Hospital General de Tomelloso, Tomelloso
University Hospital Virgen Macarena, Seville

Sweden
Skåne University Hospital, Malmö

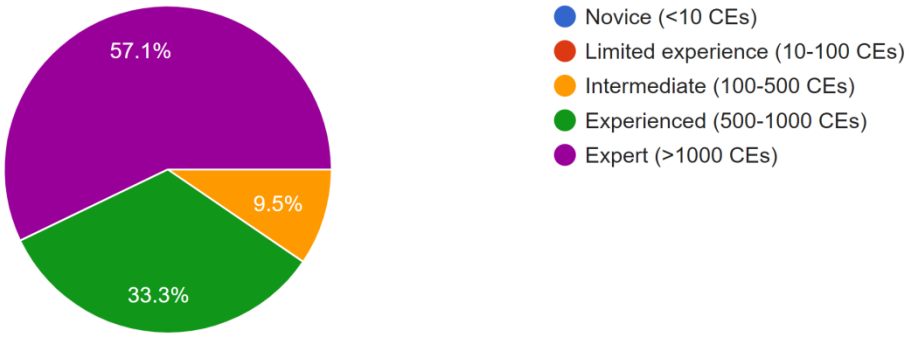
United Kingdom
Royal Hallamshire Hospital, Sheffield
The Royal Infirmary of Edinburgh, Edinburgh

Appendix III Example of the online survey platform used for the study in Chapter 8: investigating the parameters for visualisation quality in CE images



This format continued for all images presented; images were presented in a random order for each survey form filled.

Appendix IV **Details on the experience of participating CE readers in the study on visualisation quality in CE images (Chapter 8)**



Appendix V Publication resulting from the work presented in Chapter 3

Yung DE, Carvalho PB, Giannakou A, Kopylov U, Rosa B, Rondonotti E, Toth E, Plevris JN, Koulaouzidis A. Clinical validity of flexible spectral imaging color enhancement (FICE) in small-bowel capsule endoscopy: a systematic review and meta-analysis. Endoscopy. 2017;49(03):258-69.

Appendix VI Publication resulting from the work presented in Chapter 4

Yung DE, Sykes C, Koulaouzidis A. The validity of suspected blood indicator software in capsule endoscopy: a systematic review and meta-analysis. Expert review of gastroenterology & hepatology. 2017;11(1):43-51.

Appendix VII Publication resulting from the work presented in Chapter 5

Yung DE, Rondonotti E, Sykes C, Pennazio M, Plevris JN, Koulaouzidis A. Systematic review and meta-analysis: is bowel preparation still necessary in small bowel capsule endoscopy?. Expert review of gastroenterology & hepatology. 2017;11(10):979-93.

Appendix VIII Publication resulting from the work presented in Chapter 6

Yung DE, Koulaouzidis A, Douglas S, Plevris JN. Earlier use of capsule endoscopy in inpatients with melena or severe iron deficiency anemia reduces need for colonoscopy and shortens hospital stay. Endoscopy international open. 2018;6(09):E1075-84.

Appendix IX Publication resulting from the work presented in Chapter 7

Yung DE, Rondonotti E, Giannakou A, Avni T, Rosa B, Toth E, Lucendo AJ, Sidhu R, Beaumont H, Ellul P, Negreanu L. Capsule endoscopy in young patients with iron deficiency anaemia and negative bidirectional gastrointestinal endoscopy. United European gastroenterology journal. 2017;5(7):974-81.